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APRIL 1952

VOLUME 47 NUMBER 4

Published Monthly by
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Feb. 7, 1929, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $12.00

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THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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PRISMATIC EFFECT OF OBLIQUE CYLINDERS

Space does not permit us to discuss the revised oblique axis cylinder chart presented below. In the June "scientific corner," examples of its use will be given as well as cases showing the errors inherent in the previous charts.

Right Eye			Left Eye		
Axis	Vertical	Horizontal	Vertical	Horizontal	Axis
90	000	.20 out	000	.20 out	90
85	.02	.28 out	.01	.13 out	85
80	.06	.34 out	.01	.06 out	80
75	.11	.40 out	000	000	75
70	.16	.44 out	.02	.07 in	70
65	.22	.48 out	.06	.13 in	65
60	.29	.50 out	.11	.18 in	60
55	.36	.52 out	.16	.23 in	55
50	.43	.52 out	.22	.27 in	50
45	.50	.50 out	.29	.29 in	45
40	.57	.48 out	.36	.30 in	40
35	.63	.44 out	.43	.30 in	35
30	.69	.40 out	.50	.27 in	30
25	.74	.34 out	.57	.27 in	25
20	.77	.28 out	.63	.23 in	20
15	.80	.26 out	.69	.18 in	15
10	.81	.14 out	.74	.13 in	10
5	.81	.07 out	.77	.07 in	5
180	.80	000	.80	000	180
175	.77	.07 in	.81	.07 out	175
170	.74	.13 in	.81	.14 out	170
165	.69	.19 in	.80	.26 out	165
160	.63	.23 in	.77	.28 out	160
155	.57	.27 in	.74	.34 out	155
150	.50	.27 in	.69	.40 out	150
145	.43	.30 in	.63	.44 out	145
140	.36	.30 in	.57	.48 out	140
135	.29	.29 in	.50	.50 out	135
130	.22	.27 in	.43	.52 out	130
125	.16	.23 in	.36	.52 out	125
120	.11	.18 in	.29	.50 out	120
115	.06	.13 in	.22	.48 out	115
110	.02	.07 in	.16	.44 out	110
105	000	000	.11	.40 out	105
100	.01	.06 out	.06	.34 out	100
95	.01	.13 out	.02	.28 out	95
90	000	.20 out	000	.20 out	90

Calculated for + 1.00 D cylinder. All vertical figures are base up. Horizontal as marked. In using this chart, transpose all cylinders to plus.

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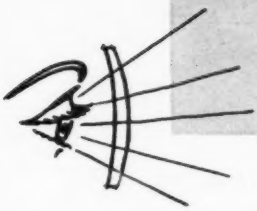

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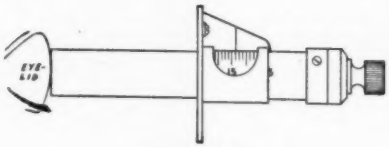

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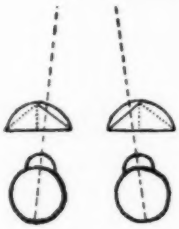

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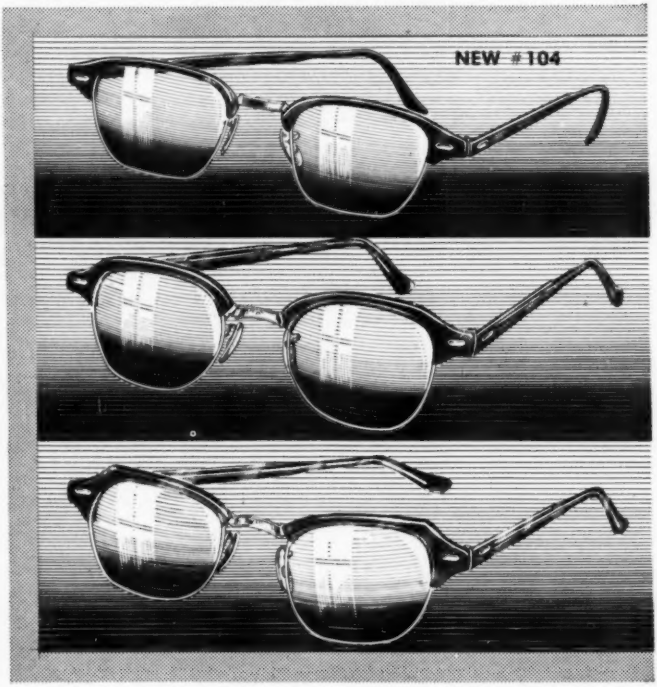

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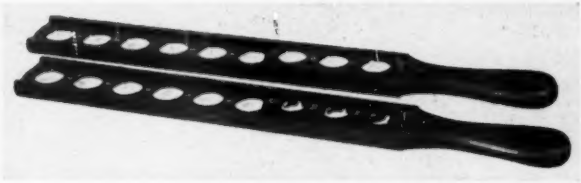

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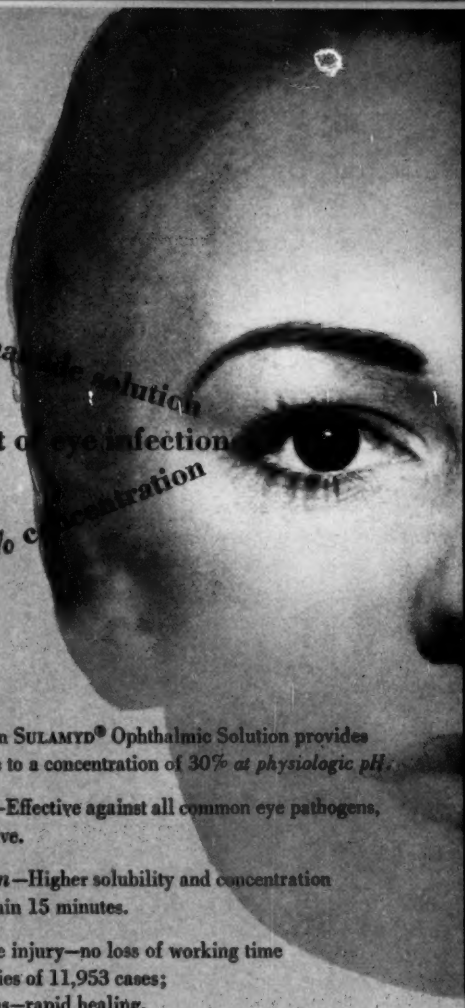

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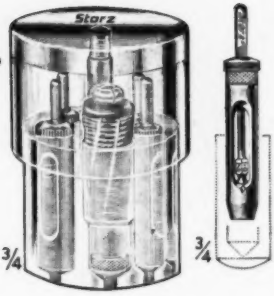

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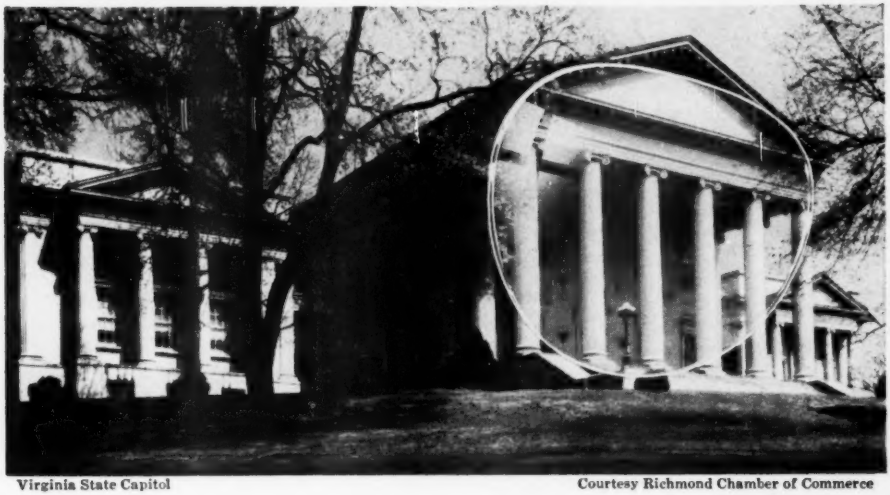

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	A	B	C	D	TINT	A	B	C	D	A	B	C	D
CORRECTED CURVE SINGLE VISION	X	X	X	*	X	*	*	*		X	X	X	*
PERFEX SINGLE VISION	X	X	X	X		X	X	X	X	X	X	X	X
KRYPTOK BIFOCALS	X	X	X	*	X	X	X	X	*	X	X	X	*
FINISHED MENISCUS KRYPTOK BIFOCALS	X	X	*	*		*	*	*	*	*	*	*	*
BONVUE "D" BIFOCALS	X	X	*	*		*	*	*	*				
STRAIGHT TOP BIFOCALS, Style C	X	X			X	*				*	*	*	
STRAIGHT TOP RIBBON SEG BIFOCALS, Style M or N	X	X				*				*	*	*	
STRAIGHT TOP TRIFOCALS	X	X			*	*				*	*	*	
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1. Scheie, H. G., Tyner, G. S., Buesseler, J. A., and Alfano, J. E., *J. A. M. A. Arch. Ophth.* 45:301, March 1951.

2. Leopold, I. H., Purnell, J. E., Cannon, E. J., Steinmetz, C. G., and McDonald, P. R., *Am. J. Ophth.* 34:361, March 1951.

Literature on request

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ARCHIVES OF OPHTHALMOLOGY

VOLUME 47 APRIL 1952 NUMBER 4

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Editorials

INTERGROUP RESEARCH

The possibilities of intergroup research in ophthalmology became strikingly apparent during World War II. Then, under the able leadership of Jonas Friedenwald and the sponsorship of the War Gas Casualties Committee, several laboratories were united in an attempt to find an effective antidote for mustard-gas burns of the eye. None was found, but much fundamental information was obtained on the metabolism of the cornea and on the toxicologic reactivity of biologic tissue in general. What was perhaps more significant was the fact that the energies of various research groups could be so harmoniously directed to a common ophthalmological goal.

But things were different then. The war was on, and those who, for one reason or another, remained in the laboratory, while their brothers joined the regular services, were anxious to contribute to the full capacity of their talents. It is, therefore, the more remarkable that a similar coordination of research groups has been carried over into the present. This time it is for the study of radiation cataract, and the sponsoring agent is the Atomic Energy Committee.

The sub-Committee on Radiation Cataract has just held its third annual meeting. These sessions have been conclaves of biologists, biochemists, physicists, and ophthalmologists. As with the mustard-gas project, it seems fair to predict that no effective cure for radiation cataract will be found, but doses of radiation and types of irradiation that can cause cataracts have been defined; the lens has been found an extraordinarily suitable test object for studying the biologic reactivity to irradiation, and much information has been obtained on basic biochemical processes in the lens that will have applicability to cataracts in general.

These two major ventures of intergroup collaboration in ophthalmological research have been successful. But the potential pitfalls in intergroup research are also considerable. With research operated on a large scale, organization may become the end in itself, with corresponding de-emphasis on the essential individual. Bureaucratic support for research may result in the parceling out of funds to those who have composed the most seductive euphemisms rather than to those who have shown the greatest talent in research. Examples of this unfortunate, but seemingly inevitable, by-product of centralization will no doubt be repeatedly evident in the future, as has occasionally been the case in the past. Let us hope that there will also continue to be examples like the two ventures here cited, in which the quality of the research has been the only significant consideration.

DAVID G. COGAN, M.D.

EXPERIENCES WITH TUMORS OF THE RETINA

KENNETH C. SWAN, M.D.
AND
SELMA HYMAN, M.D.
PORTLAND, ORE.

THIS is the fourth in a series of reports concerning experiences with tumors of the eye and its adnexa.[1] It has not been our purpose to review the literature or to cover the subjects completely; rather, by discussing from personal experiences some aspects that have received little attention or have been subject to controversy, it has been the intention of our faculty to contribute to the improved clinical management of ocular tumors.

Retinal tumors of non-neoplastic origin are relatively frequent. These are primarily proliferative responses to injury, organization of exudates, or the formation of cysts in the retina. In addition, there are a number of conditions that may result in elevation of either the retina or the pigment epithelium or both. These conditions often simulate neoplasms and therefore must be considered in a differential diagnosis.

True neoplasms of the retina are limited in type and occur infrequently. Metastatic involvement of the retina must be extremely rare. Only one metastatic neoplasm, from an adenocarcinoma of the breast, was observed in our laboratory and clinical services over a seven-year period. Invasion or disturbance of the retina by tumors of the other structures of the eye is much commoner and will be discussed in a subsequent publication concerned with choroidal tumors. Neoplasms of the retina associated with other diseases, notably the phacomatoses, seem to occur more commonly than metastases, but also are rare. In the last five years two patients with tuberous sclerosis have been observed to have retinal tumors. Two children with angiomatous tumors of the retina in association with similar cerebellar lesions were also observed.

Proliferation and metaplasia of the pigment epithelium were commonly noted in eyes enucleated after long-standing injuries or inflammation, but in a study of

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From the Departments of Ophthalmology and Radiology, University of Oregon Medical School.

This study is part of studies conducted under grants from the Damon Runyon Cancer Fund and the American Cancer Society.

Presented at the Thirty-Seventh Annual Clinical Congress of the American College of Surgeons, San Francisco, Nov. 8, 1951.

1. Browning, C. W., and Swan, K. C.: Experiences with Some Tumors of the Iris, Tr. Pacific Coast Oto-Ophth. Soc. **32**:3-27, 1948. Swan, K. C.; Emmens, T. H., and Christensen, L.: Experiences with Tumors of the Limbus, Tr. Am. Acad. Ophth. **52**:458-469 (May-June) 1948. Reeh, M. J., and Swan, K. C.: Experiences with Tumors of the Lid, ibid. **54**:312-325 (March-April) 1950.

more than 500 specimens in the John E. Weeks Memorial Laboratory in Ophthalmology no malignant neoplasms were observed to arise from the pigment epithelium.

The vascular system of the retina occasionally is the source of primary tumors. Two children and one adult with unilateral angiomatous tumors limited to the retina have been observed in the clinic in recent years. In one boy, the tumor was limited to the temporal periphery and was successfully controlled by application of an undamped diathermy current to the tumor through scleral perforations. Unfortunately, edema and exudation in the macular region had seriously impaired central vision before surgical intervention. In the other patients, the tumor was far advanced, and enucleation was required for relief of pain from the secondary glaucoma.

Both sentient and supporting structures of the retina have a common neuroectodermal origin; however, well-differentiated gliomas of the retina are extremely rare. Not a single specimen of true glioma of the retina has been received in our laboratory. By far the commonest primary neoplasms of the retina observed were the malignant growths classified as retinoblastoma. These seem to arise from undifferentiated or poorly differentiated primitive cells. Subclassifications have been described, but all such neoplasms seem to consist, at least in part, of this basic cell type.

During the past seven years 25 patients with retinoblastoma confirmed by histologic study have been observed by the faculty of the University of Oregon Medical School. The history and examination were incomplete for 5 patients, but our experience with the remaining 20 provides pertinent data concerning the diagnosis and management of this important neoplasm.

There is considerable evidence to indicate that hereditary factors are important in retinoblastoma. Observation of our patients has not been sufficiently prolonged to enable us to evaluate this factor, but in only 1 of the 20 cases was there a history of retinoblastoma in a second member of the family. In this instance father and daughter had bilateral tumors.

Twelve of our 20 patients with retinoblastoma had bilateral tumors. This supports Reese's contention that the generally accepted figure of a 25% incidence of bilateral involvement is too low.[2] It is quite possible that subsequent examination may reveal a tumor developing in the second eye of several of our recently observed patients with unilateral retinoblastoma. It is our custom to reexamine these patients at three- to four-month intervals; however, we have yet to find involvement in the second eye which was not recognized at the patient's first admission.

A summary of the findings on admission in our 20 patients indicates that in the Pacific Northwest, at least, treatment of retinoblastoma is generally begun at a tragically advanced state of the neoplasm. In seven of the eight cases of unilateral involvement the growth was so far advanced that there was loss of all useful vision in the affected eye. In four of these eyes histologic study revealed invasion of the optic nerve by the tumor. Seven of the 12 patients with bilateral involvement were blind, or practically blind, at the time of admission. In all seven patients there was

2. Reese, A. B.: Tumors of the Eye, New York, Paul B. Hoeber, Inc., 1951.

histologic evidence of the invasion of the optic nerve at the time of enucleation of the most involved eye. Of the remaining five children, three had small peripheral tumors, but in two others there were neoplasms which filled at least one-fourth of the vitreous cavity. In summary, there was histologic evidence of extraocular extension of the tumor in more than one-half of the 20 patients.

The only early symptom of retinoblastoma would be some disturbance of vision in one eye; unfortunately, almost all the patients were infants and small children too young to complain to parents about visual disturbances. Even in cases of bilateral retinoblastoma one eye is almost always involved earlier than the other. Marked impairment in vision was noted as an early sign in only 1 of our 20 patients. An abnormal appearance of the eye, rather than evidence of impaired vision or complaint of pain, made the parents seek medical advice. Inequality of the pupils was the first sign noted by the parents of 10 of the 20 patients. In six children a strabismus of variable degree was the first sign noted. Enlargement of one eyeball due to secondary glaucoma was the first abnormality noted by the the parents of three children. The appearance of the tumor behind the pupil or an abnormal

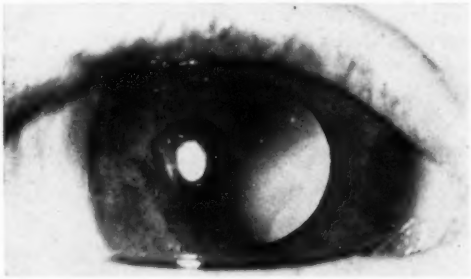

Fig. 1.—Reflection of light from the surface of a retinoblastoma.

pupillary reflection from the surface of the tumor was generally observed months after the other signs (Fig. 1). The classic sign of a yellow mass behind the pupil, i. e., the amaurotic cat's-eye, was noted as the first sign by the parents of only one child. It is noteworthy that, with one exception, the neoplasm had invaded the optic nerve in every enucleated eye which had had this classic sign.

From the foregoing discussion, it is evident that early in the course of retinoblastoma formation, symptoms and gross outward signs are lacking. Early diagnosis, therefore, must depend upon the recognition that pupillary inequality, persistent ocular deviations, difference in size of the eyeball, abnormal pupillary reflections, and similar signs may be of great significance when observed in an infant. Our experience indicates that this is not general. The majority of parents first consulted a physician other than an ophthalmologist. In more than one-half the cases there was a period of observation or reassurance, lasting four months or longer, before referral to an ophthalmologist was recommended. This was particularly true of the infants who showed no external signs other than pupillary inequality or the presence of heterotropia. In several instances the parents were advised that such findings were common in babies and took their

children home until more alarming signs developed. Ophthalmologists of the Pacific Northwest seem quite aware of retinoblastoma and its diagnostic features. During the past five years not a single specimen has been received in the John E. Weeks Memorial Laboratory in which the retinoblastoma was undiagnosed.

Differential diagnosis of early retinoblastoma seems relatively easy, because the ocular media remain clear and the lesion has rather typical features. Even if the tumor or tumors are flat and are of the so-called exophytum type, the closely packed cells cause a typical focal loss of the normal transparency of the retina. The small lesions appear ghostly white, owing to their relative avascularity. The classic cat's-eye yellow or the "creamy" discoloration described by Reese was observed only in the case of a relatively large growth.

In two of our patients with advanced tumors in one eye, small neoplasms in the second eye were not discovered when the infants were examined in the clinic by direct ophthalmoscopy, even though the pupils were widely dilated and the patient was under sedation. When these infants were examined under anesthesia with the eye forcibly rotated and stabilized, small tumors were noted in the peripheral retina. In relatively nonpigmented eyes such tumors may be difficult to recognize because there is little contrast between the white tumor and the underlying pale sclera. A standard binocular ophthalmoscope, dismantled from its stand and held in the hand, is useful in detecting small elevations. The usual 10-power Huygenian eyepieces are replaced by the 5-power, wide-field type of oculars to widen the field of vision and increase the depth of focus.

In the advanced cases differential diagnosis often becomes more difficult because complications, such as degenerative uveitis and glaucoma, may dominate the clinical picture and obscure the tumor. Then retinoblastoma must be differentiated from all other lesions producing either extensive separation of the retina or any type of inflammatory or congenital mass behind the lens. Transillumination is often disappointing in the differential diagnosis of retinoblastoma from these other conditions, in which large hemorrhages may occur in the interretinal space. A localized collection of blood may block the transmission of light, whereas globes containing a relatively large retinoblastoma may transilluminate well, owing to the fact that the tumor, unlike the malignant melanoma of the choroid, is not pigmented and often is not in direct contact with the sclera, owing to separation of the retina. This was the circumstance observed in two eyes which transilluminated well, but which after enucleation were found to contain relatively large tumors. In both eyes there was room for light to spread around the tumor.

It has been known for many years that a large percentage of retinoblastomas have areas of degeneration containing calcium. X-ray studies of the orbit for evidences of intraocular calcification are therefore of most value in establishing the diagnosis in advanced cases with cloudy media. Roentgenologic evidence of intraocular calcification was present in 18 of 23 eyes with retinoblastoma, but it must not be considered pathognomonic. Multiple small intraocular calcifications were found by means of x-rays in two children with other causes of extensive separation of the retina and secondary glaucoma. In one child the histologic picture was that of external exudative retinitis. In the other child there was retinal separation with extensive gliosis and proliferation and metaplasia of the pigmented epithelium.

Apparently, calcifications are relatively common in any type of degenerative process in the posterior segment of infants' eyes.

It should not be concluded that the roentgenogram does not show calcifications unless the roentgenologist is certain that the eye was motionless at the time of the exposure and that exposure was properly made. It is also important that multiple exposures be made. In this clinic five films are considered minimal for exclusion of the presence of calcification. In one case the calcifications were not observed in films taken with the child under light sedation but were readily detected when the roentgenograms were repeated with the child under anesthesia and the eye was stabilized. Details of technique have been described by Pfeiffer.[3]

It might be thought that histologic study of an eye with retinoblastoma would establish the diagnosis with certainty, but this was not the case with two children who had had enucleations of a blind eye in a general hospital. In both instances inadequate preparation and study of the specimen resulted in the tumor's being overlooked. In one case the globe was opened by the surgeon, and only a "suspicious" section was sent to the laboratory. This section contained evidences of chronic inflammation, but no neoplastic tissue was observed. In the other case the whole eye was sectioned but was studied inadequately. The nature of the ocular pathology became evident when orbital metastases developed. Retinoblastoma may have multiple points of origin in the retina and may even cause retinal separation without formation of gross tumors. This type of lesion may be confused with a traumatic or an infectious process in gross inspection of the open globe. Proper fixation and mounting of the entire specimen with preparation of multiple sections seem essential to establish the diagnosis and to determine the presence or absence of extraocular extension.

There was not a single patient with unilateral tumor who retained useful vision in the involved eye at the time of admission; consequently, our staff was not faced with the consideration of any treatment other than enucleation in these cases. The involved eye was enucleated, with removal of the orbital portion of the optic nerve and its sheaths. The nerve was severed as far behind the globe as was possible. Then, after removal of the eye, the stump of the nerve and its sheath were picked up, and the remainder of the orbital part was removed.

Our experience is too limited to permit us to judge whether postoperative irradiation of the orbit should be done routinely after enucleation. For the present, at least, we have adopted the same policy as Reese. Neither exenteration nor postoperative irradiation of the orbit is undertaken unless there is histologic evidence of extraocular extension of the tumor. As yet, we have not observed an orbital recurrence in any case in which the optic nerve was not involved. The method of histologic study of the nerve is important; otherwise, invasion by the tumor may be overlooked. It is commonly stated that retinoblastoma spreads into the brain by direct extension; however, extension along the septa of the nerve may be tenuous and difficult to detect unless the nerve and its sheaths are studied in both longitudinal and cross sections. This requires that the nerve be divided into several parts, with cross sections made at the ends. One of our cases illustrates the

3. Pfeiffer, R. L.: Roentgenographic Diagnosis of Retinoblastoma, Arch. Ophth. **15**:811-821 (May) 1936.

importance of this procedure. In this case, sections of the nerve made on the day of operation did not reveal the tumor, but some weeks later, when pyroxylin sections of the entire globe were studied, it was noted that the lamina cribrosa had been penetrated. Additional sections were then made of the optic nerve, and an island of tumor cells was found posteriorly.

There is considerable evidence to indicate that retinoblastoma can be destroyed by radiation therapy. Irradiation of the orbit seems preferable to exenteration when the tumor invades only the optic nerve because there is a better chance of destroying tumor tissue which has reached, or is near, the optic canal. In one unilateral case an island of tumor cells was noted in the optic nerve at the point of entrance of the central artery. Postoperative irradiation to the orbit was completed

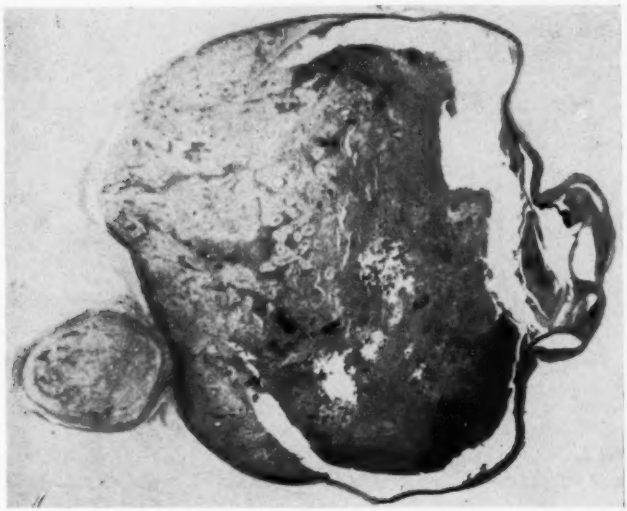

Fig. 2.—Retinoblastoma almost filling the globe. The choroid and optic nerve are invaded. Focal areas of necrosis and calcification are present on the anterior part of the tumor.

more than a year ago. There is no evidence of persistent or recurrent tumor, and the child is wearing a prosthesis. Exenteration has not seemed indicated in any of our cases, but was considered in several.

At least one eye was enucleated in all 12 patients with bilateral retinoblastoma. Histologic study of the enucleated eye of six patients revealed large growths and extension of the tumor into the optic nerve (Fig. 2). Four of these patients have died of metastases, and another has recently shown evidence of extraorbital lesions. Of the remaining six children with bilateral involvement, but without evidences of extraocular extension, only one retained useful vision in both eyes. This child had multiple small tumors and partial separation of the retina bilaterally. To confirm the diagnosis and to justify extensive radiation therapy to the other eye, the attending ophthalmologist enucleated the more involved eye. This child is receiv-

ing x-ray treatment. In five other patients, involvement in the second eye seemed limited to one part of the posterior segment, and there was no evidence of metastases. In these patients there was hope of destroying the tumor, with retention of vision and without radiation damage to the vulnerable anterior segment. These five patients have been treated by a modified Reese-Martin technique. Two have survived more than five years with the retention of nearly normal visual acuity (Fig. 3). The two other patients have retained good vision but have been observed for shorter periods. Details of these successfully treated patients will form the basis of a subsequent report. In the fifth child secondary glaucoma had become manifest before the radiation was undertaken. The therapy was completed, but the eye had to be enucleated for relief of pain from the glaucomatous process.

Fig. 3.—Calcified remnant of a retinoblastoma five years after completion of radiation therapy.

Histologic study of the enucleated eye revealed the tumor to have been completely destroyed. This child has survived and is still healthy, six years after enucleation of the second eye.

Our technique will be reported in detail later. It is based on principles elaborated by Reese and Martin.[2] A large tumor dose is achieved by directing the beam through two or more small ports, care being taken to avoid the anterior segment. Daily treatments with relatively small doses have permitted successful regeneration of normal tissue. Such treatment requires the utmost cooperation of the ophthalmologist and the roentgenologist. Both must win the confidence and assistance of the patient and the parents. The primary role of the ophthalmologist is accurate localization of the tumor for the roentgenologist and observation of results, but it is the responsibility of the roentgenologist to determine the dosage and treatment schedules.

The above-described experiences indicate that there is effective treatment for retinoblastoma but that it must be begun early in the course of the condition. This means more than early diagnosis. It also requires that the parents have full confidence in the physician and promptly accept his recommendations for therapy. In our series of patients, there were several tragic delays in the institution of therapy after the diagnosis was established. These delays emphasize the need for the ophthalmologist to give attention to the psychologic management of the parents, as well as to the medical aspects of the case. He must recognize that retinoblastoma is a condition which tends to create intense emotional reactions in the parents and their well-meaning friends. These emotions are apt to be greatly intensified if consulting ophthalmologists frankly express differences of opinion regarding therapy.

Final responsibility for the decision to proceed with treatment must be assumed by the parents; however, the decision to have the eye of a precious baby removed is difficult for parents to make alone. Without assuming undue responsibility, the ophthalmologist and his consultants can often give enough sympathetic guidance to enable the family to meet their problem rationally. Otherwise, the press will continue to dramatize the plight of parents reputedly left by physicians to choose between "life or sight" for their child. In reality, such a choice should never be required, because failure to treat the ocular condition almost invariably means loss of life.

Our experience indicates that few parents will accept bilateral enucleation as a primary procedure for their baby. Prior to their referral to the University of Oregon Medical School, bilateral enucleation was recommended by various ophthalmologists to the parents of five of our patients. In all instances, this advice was rejected, and the institution of treatment was unnecessarily delayed. On admission, the same parents were willing to have the more involved eye removed for histologic confirmation of the diagnosis, but as long as there was the slightest possibility of error they would not permit enucleation of both eyes at the first operation. With all uncertainty about diagnosis eliminated by enucleation and histologic study of one eye, the parents of these five children were better able to consider recommendations concerning the second eye. In three instances removal of the second eye was recommended and the parents approved.

SUMMARY AND CONCLUSIONS

Experiences with tumors of the retina are reviewed. Retinoblastoma seems one of the most important malignant tumors of infancy, but often treatment is not begun until the tumor has progressed to an advanced state. Extraocular extension was confirmed by histologic study in one-half the eyes enucleated for retinoblastomas. Pupillary inequality and persistent strabismus were the common early signs in 20 patients. The public and physicians must be made aware that in infants these signs often indicate serious disease of the eye.

Twelve of the 20 patients with retinoblastoma had bilateral tumors. With one exception, the tumor was much more advanced in one eye. Examination with the child under anesthesia with the pupil dilated and the eye stabilized is essential to the detection of early peripheral lesions. Binocular indirect ophthalmoscopy is recommended. Differential diagnosis of the advanced stage of retinoblastoma also

may be difficult because signs of the tumor are often obscured by complications, such as secondary glaucoma and uveitis. Transillumination is often misleading. X-ray evidence of intraocular califications is helpful but is not pathognomonic of retinoblastoma.

Early surgical treatment alone or with irradiation offers hope for preservation of life and vision. Unfortunately, institution of treatment is often delayed even after the diagnosis has been made. Good psychologic management of the parents is particularly important in eliminating these tragic delays. Most parents, hoping for an error in diagnosis, will reject a recommendation of bilateral enucleation as a primary procedure. In contrast, all seem willing to permit enucleation of the more involved, and usually blind, eye in order that the diagnosis may be established with certainty.

Only 6 of 12 patients with bilateral retinoblastoma were admitted with enough vision to justify treatment of the better eye with x-ray therapy. After having been treated by a modification of the Reese-Martin technique, two children have survived more than five years with retention of nearly normal vision. Three other children have retained good health and vision, but have been observed for shorter periods. The sixth child lost his vision from progression of preexisting glaucoma. Histologic study of the enucleated eye revealed the tumor to have been completely destroyed.

TOXOPLASMA CHORIORETINITIS IN ADULTS

A Preliminary Study of Forty-One Cases Diagnosed by Microscopic Examination

HELENOR CAMPBELL WILDER
WASHINGTON, D. C.

ORGANISMS having the morphologic characteristics of Toxoplasma, some appearing in pseudocysts, have been identified in chorioretinal lesions in 41 eyes removed from patients between the ages of 16 and 72 years. Twenty-seven of these patients were males and 14 were females; 40 were white, and 1 was a Negro. The lesions were unilateral, although in one instance scars of old choroiditis had been observed clinically in the opposite eye. In one patient chorioretinitis followed childbirth. One patient had mild diabetes; one, rheumatoid arthritis; one, a history of severe tonsil and tooth infection, and another, a history of gall bladder attacks and heart decompensation. One patient had a sore throat when chorioretinitis was first noted. An inguinal-node lesion which was histologically similar to that in the eye was found in another patient. As far as could be determined, 34 patients were free from symptoms of disease apart from the eye; however, 9 gave a history of direct injury which had preceded the onset of ocular symptoms at varying intervals. In six instances these injuries were nonpenetrating. The duration of ocular symptoms varied from 1 month to 32 years.

The lesions were strikingly uniform, and their granulomatous character, together with marked necrosis, had in many instances led to a pathologic diagnosis of tuberculosis or possible tuberculosis. Pseudocysts and organisms were recognized in paraffin sections, but the characteristic cresentic forms of the protozoa were most clearly demonstrated by oil-immersion examination of celloidin sections stained with hematoxylin and eosin.

Continued study of material in the Registry of Ophthalmic Pathology is expected to reveal additional cases of Toxoplasma chorioretinitis. Through the cooperation of the contributors and of Dr. Leon Jacobs, of the National Institutes of Health, an attempt is being made to correlate serologic and pathologic findings. A more complete report is in preparation, with detailed clinical and pathologic data, histologic description of the lesions, and photomicrographs of sections showing the organisms and the inflammatory reaction they evoke.

From the Armed Forces Institute of Pathology.

Submitted for publication Jan. 5, 1952.

EFFECTIVENESS OF TERRAMYCIN AND OTHER ANTIBIOTICS AGAINST EXPERIMENTAL BACTERIAL KERATITIS

EDWARD J. CANNON, M.D.
AND
IRVING H. LEOPOLD, M.D.
PHILADELPHIA

THIS STUDY was undertaken to evaluate the new antibiotic terramycin. This was done by simultaneous comparison with other agents, namely, neomycin, chloramphenicol (chloromycetin®), aureomycin, and streptomycin, against standard pure-culture corneal infections of the rabbit eye. Terramycin has a wide antibacterial spectrum (Table 1).[1]

TABLE 1.—*Species of Bacteria Susceptible to the Action of Streptomycin in Vitro*[1]

Hemolytic streptococci	Corynebacterium diphtheriae (some strains)
Str. agalactiae	C. pseudodiphtheriticum (hofmanni)
Str. dysgalactiae	C. xerose
Str. equi	Mycobacterium tuberculosis
Streptococcus faecalis	Myco. smegmatis
Streptococci of viridans group	Myco. ranae
Diplococcus pneumoniae	Myco. phlei
Staphylococcus aureus	Myco. avium
Staph. albus (some strains)	Clostridium perfringens (welchii)
Micrococcus flavus	Cl. botulinum
Sarcina lutea	Cl. sporogenes
Bacillus subtilis	Cl. tetani
B. circulans	
B. anthracis	
Neisseria catarrhalis	Escherichia coli
N. meningitidis	Aerobacter aerogenes
N. gonorrhoeae	Klebsiella pneumoniae
H. influenzae	Salmonella typhosa
pertussis	S. paratyphi
Brucella bronchiseptica	S. dysenteriae
Br. abortus	S. typhimurium
Br. suis	S. sp. (Type Newport)
Br. melitensis	S. enteritidis
Pasteurella pestis	S. choleraesuis
Past. tularensis	S. pullorum
Serratia marcescens (some strains)	Pseudomonas aeruginosa (pyocyanea) (some strains)
Vibrio comma	

From the Research Department of the Wills Hospital.

Presented at the Third Wills Hospital Conference, March 16, 1951.

Thesis submitted by Dr. Cannon to the Faculty of the Graduate School of Medicine of the University of Pennsylvania in partial fulfilment of the requirements for the degree of Master of Medical Science (M.Sc. Med.).

1. Hobby, G.; Lenert, T. F.; Pikye, V.; Kifeleck, M., and Hudders, M. E.: Antimicrobial Microaction of Terramycin, Ann. New York Acad. Sc. **53**:266, 1950. Bliss, E. A.; Warth, P. T.; Chandler, C. A., and Long, P. H.: Studies of Terramycin in Vivo and in Vitro, Bull. Johns Hopkins Hosp. **87**:171, 1950. Bliss, E. A.; Warth, P. T., and Chandler, C. A.: Susceptibility of Gram-Positive Cocci, Gram-Negative Bacilli and Clostridia to Terramycin, Ann. New York Acad. Sc. **53**:277, 1950.

In studying the course and treatment of corneal ulcers, it has been found that the eyes of experimental animals lend themselves well to the production of standard infections which can be accurately observed.[2]

The organisms selected for the present study were chosen for their resistance to the commonly employed therapeutic agents and their ability to produce corneal ulcerations of desired severity (Table 2).

METHOD

Preparation of the Organsim.—After centrifuging a pure 18-hour trypticase-soy broth culture of a strain of Pseudomonas aeruginosa, the supernatant fluid was decanted and sterile isotonic solution of sodium chloride was added to the packed organisms. The organisms were then dispersed evenly throughout the solution. Once more the organisms were centrifuged and the supernatant fluid decanted. Enough sterile isotonic solution of sodium chloride was added to the packed organisms that the final nephelometer reading of the suspended bacteria was 600,000,000 organisms per cubic centimeter of sterile isotonic solution of sodium chloride.

Similarly, sterile suspensions of Aerobacter aerogenes, Escherichia coli, and Proteus vulgaris were prepared from 18-hour trypticase-soy broth cultures. However, the latter organisms gave

TABLE 2.—*In Vitro Sensitivities (Turbidimetric Method)* *

Organism Employed in Production of Corneal Ulcers		Terramycin	Aureomycin	Strepto-mycin	Neomycin	Chlor-amphenicol	Penicillin
Ps. aeruginosa		8-10	Resistant	Resistant	5	2-4	Resistant
A. aerogenes		2.5	10	5	0.6	5	Resistant
Esch. coli		5	Resistant	10	2.5	Resistant	Resistant
P. vulgaris		0.3	Resistant	Resistant	2.5	Resistant	Resistant
Staph. aureus	24 hr.	1	1	20†	5	5	Resistant
	48 hr.	5‡	5	20	5	10	to 5
D. pneumoniae	24 hr.	1	1	15	15§	5‖	0.5
	48 hr.	1	1	15	15	5	0.5
Hemolytic streptococci	24 hr.	1	1¶	Resistant	10	5	0.1
	48 hr.	1	5	to 20	10	5	0.1

* Values expressed in micrograms per milliliter of the antibiotic.
† Staphylococcus (24 hr.): Partial inhibition by 15 U. (1.32 γ) per milliliter of streptomycin.
‡ Staphylococcus (48 hr.): Over 50% inhibition by 1 U. (1.0 γ) per milliliter of terramycin.
§ D. pneumoniae (24 hr.): 90% inhibition by 10 U. per milliliter of neomycin.
‖ D. pneumoniae (24 hr.): Partial inhibition by 1 U. (1.0 γ) per milliliter of chloramphenicol.
¶ Generally speaking, the 48-hour sensitivity reading is a truer sensitivity value with the bacteriostatic drugs, but not if the drugs are bactericidal. However, aureomycin is labile on incubation, and therefore the 24-hour sensitivity reading is more accurate than the 48-hour reading, since aureomycin loses 50% of its potency after 24 hours of incubation.

a nephelometer reading of 800,000,000 organisms per cubic centimeter of sterile isotonic solution of sodium chloride.

Saline suspensions of Type I Diplococcus pneumoniae, coagulase-positive Staphylococcus aureus, and hemolytic streptococci failed to produce corneal ulcers in the rabbit eye. Therefore

2. (*a*) Joy, H. H.: Treatment of Experimental Bacillus Pyocyaneus Ulcer of the Cornea with Sulfapyridine, Tr. Am. Ophth. Soc. **39**:456, 1941. (*b*) von Sallmann, L.: Sulfadiazine Iontophoresis in Pyocyaneus Infection of the Rabbit Cornea, Am. J. Ophth. **25**:1292, 1942. (*c*) Robson, J. M., and Scott, G. I.: Local Chemotherapy in Experimental Lesions of the Eye Produced by Staphylococcus Aureus, Lancet **1**:100, 1943. (*d*) Brown, A. L., and Pugh, J.: Effect of Intra-Ocular Concentration of Typhoid Antibodies on Experimental Corneal Ulcers: with Report of 7 Cases, Arch. Ophth. **16**:476 (Sept.) 1936. (*e*) Robson, J. M., and Scott, G. I.: Production and Treatment of Experimental Pneumococcal Hypopyon Ulcers in the Rabbit, Brit. J. Exper. Path. **24**:50, 1943; (*f*) Local Treatment of Experimental Pyocyaneus Ulcers of the Cornea with Albucid Soluble, Nature, London **148**:167, 1941. (*g*) Leopold, I. H.; Holmes, L., and LaMotte, W. D., Jr.: Local Versus Systemic Penicillin Therapy of Rabbit Corneal Ulcer Produced by Gram-Negative Rod, Arch. Ophth. **32**:193 (Sept.) 1944.

these organisms were not given a saline washing: Instead, the beef brain-heart broth of 18-hour cultures with a nephelometer reading of 800,000,000 organisms per cubic centimeter of broth was employed.

It is readily apparent from Table 2, illustrating the in vitro sensitiveness of these organisms, that they were chosen for their resistance to many of the antibiotics in common use. These organisms were in every instance isolated from human infections.

To make sure that pure-culture infections were being produced, smears and cultures were made from the solutions of bacteria just prior to their intracorneal injection.

Injection of sterile trypticase-soy broth in the rabbit cornea produced an area of localized edema which disappeared within 24 hours.

Intracorneal injections of beef brain-heart broth also produced an area of localized edema that disappeared within 24 hours.

TABLE 3.—*Scale of Grading Severity of Ocular Lesions Produced by Inoculated Bacteria*

		Maximum Point
Conjunctiva		
Redness		2
Chemosis		2
Discharge		2
Cornea		
Duration of activity		3
1 to 4 days	1	
4 to 6 days	2	
6 to 10 days	3	
Infiltration		2
Area of cornea involved		4
Vascularization—intensity and length		4
Ulceration		
Stain with fluorescein	1	
Visible ulceration	2	
Deep slough	3	
Perforation	4	8
Edema		4
Iritis		
Small pupil, photophobia and flare	1	
Congestion of iris and dense flare	2	
Exudation	3	3
		34 = 100% lesion

Method of Injection.—Albino and blue- and brown-eyed chinchilla rabbits, each weighing 2 to 3 kg., were utilized in these experiments.

Using a sterile 26-gauge needle and tuberculin syringe, approximately 0.02 cc. of the suspended bacteria was injected intracorneally.

Topical anesthesia with 0.5% tetracaine hydrochloride was found to be adequate for these corneal injections.

The injections of Ps. aeruginosa were the only ones made with the rabbit under general anesthesia induced with 25 mg. of sodium pentobarbital [3] per kilogram of body weight.

The eyes were stained daily with fluorescein sodium, 2%.

Smears and cultures were taken on the third, sixth, and ninth days from the cornea and cul-de-sacs of the rabbits.

Photographs of the corneal lesions were taken at varying time intervals during the 10 days of the experiments.

3. Administered as "veterinary nembutal® sodium," containing 60 mg. of phenobarbital, 10% alcohol, and 20% propylene glycol in water.

Enucleations in preparation for microscopic study were carried out at the conclusion of the experiments.

In order to evaluate the data concerning these experimental bacterial infections, arbitrary scores were assigned to each lesion according to a method previously employed. Observations on

TABLE 4.—*Organisms and Antibiotics Tested*

Organism	No. of Eyes Treated	No. of Eyes Control	Drug Tested	Concentration	Time of Onset of Therapy After Inoculation (Hr.)
Ps. aeruginosa	4	4	Terramycin	0.5 mg./cc. 10 mg./gm.	1
	4	4	Terramycin	5 mg./cc. 30 mg./gm.	1
	4	4	Terramycin	0.5 mg./cc. 10 mg./gm.	4
	4	4	Terramycin	5 mg./cc. 30 mg./gm.	4
A. aerogenes	4	4	Terramycin	5 mg./cc. 30 mg./gm.	1
	4	4	Terramycin	5 mg./cc. 30 mg./gm.	4
	4	4	Neomycin	2.5 mg./cc. 5 mg./gm.	1
Esch. coli	4	4	Terramycin	5 mg./cc. 30 mg./gm.	1
	4	4	Terramycin	5 mg./cc. 30 mg./gm.	4
	4	4	Neomycin	2.5 mg./cc. 5 mg./gm.	1
P. vulgaris	4	4	Terramycin	5 mg./cc. 30 mg./gm.	1
	4	4	Terramycin	5 mg./cc. 30 mg./gm.	4
	4	4	Neomycin	2.5 mg./cc. 5 mg./gm.	1
Staph. aureus	6	6	Terramycin	5 mg./cc. 30 mg./gm.	1
	4	4	Neomycin	2.5 mg./cc. 5 mg./gm.	1
	4	4	Chloramphenicol	2.5 mg./cc. 10 mg./gm.	1
	4	4	Aureomycin	5 mg./cc. 10 mg./gm.	1
	4	4	Streptomycin	5 mg./cc. 10 mg./gm.	1
D. pneumoniae Type I	6	6	Terramycin	5 mg./cc. 30 mg./gm.	1
	4	4	Neomycin	2.5 mg./cc. 5 mg./gm.	1
	4	4	Chloramphenicol	2.5 mg./cc. 10 mg./gm.	1
	4	4	Aureomycin	5 mg./cc. 1 mg./gm.	1
	4	4	Streptomycin	5 mg./cc. 10 mg./gm.	1
Hemolytic streptococci	8	8	Terramycin	5 mg./cc. 30 mg./gm.	1
	6	6	Terramycin	5 mg./cc. 1 mg./gm.	1
	4	4	Aureomycin	5 mg./cc. 1 mg./gm.	1
	4	4	Chloramphenicol	2.5 mg./cc. 10 mg./gm.	1
	4	4	Neomycin	2.5 mg./cc. 5 mg./gm.	1
	4	4	Streptomycin	5 mg./cc. 10 mg./gm.	1

these experimental lesions were recorded three times a day. This method of scoring is illustrated in Table 3. By using this grading system, one can compare the reactions in individual eyes, as results are expressed in identical units. Statistical analysis (standard deviation) can be applied to the figures obtained, and one therefore can determine whether any therapeutic agent has had a statistically significant effect.

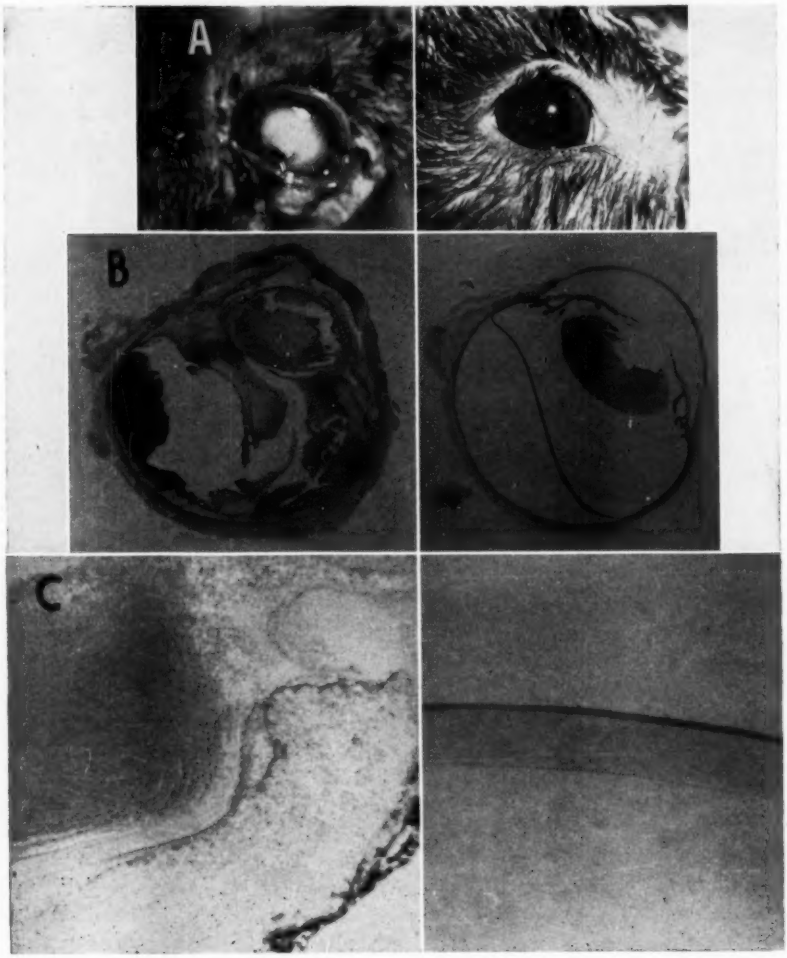

Fig. 1.—Effect of 10 days' treatment with terramycin of eyes infected with Pseudomonas aeruginosa.

In this figure, and in Figures 2 to 5, the control (left) eyes appear at the left; the treated (right) eyes, at the right. *A* shows the gross appearance of the control (untreated) and the treated eyes; *B*, the eyes after enucleation (×1.5), and *C*, sections of the eyes at point of maximal involvement (× 100).

Treatment Schedule.—Instillations of the antibiotic solutions were made upon the cornea and cul-de-sacs of the right eyes every hour for 10 consecutive hours. Ointment containing the antibiotic was applied to the right eye as the last treatment of the first day.

During the second day the solutions were instilled every hour for five hours, followed by the application of ointment twice during a five-hour period.

From the 3rd to the 10th day the antibiotics in ointment form were applied to the right eye every three hours over a daily 12-hour period.

The left eyes served as controls, receiving drops of a solution containing sodium chloride, 12.5 mg., and sodium borate, 5 mg., per cubic centimeter of distilled water. When the antibiotic

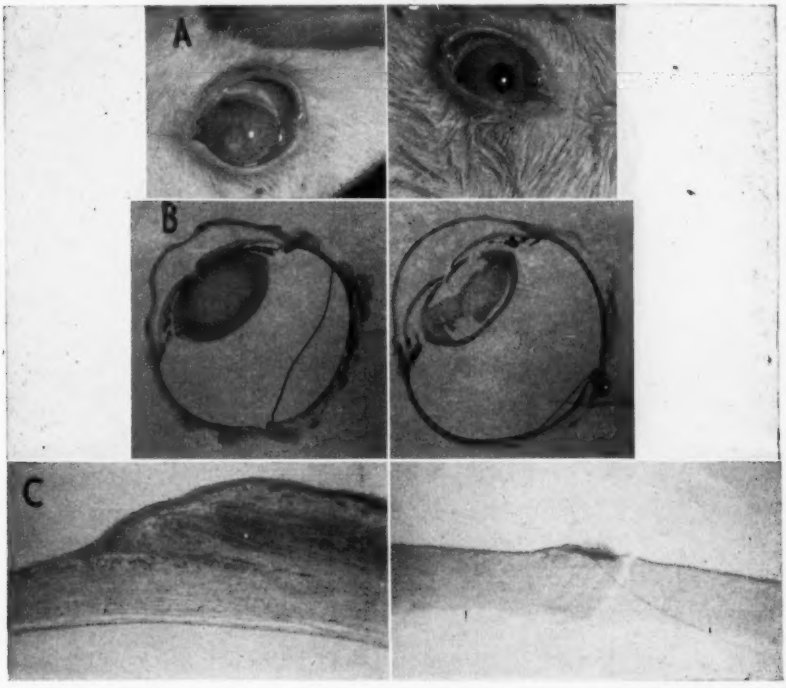

Fig. 2.—Effect of 10 days' treatment with terramycin of rabbit eyes experimentally infected with Aerobacter aerogenes.

ointment was applied to the right eye, the control eye received local applications of the ointment vehicle alone.

The organisms employed, the number of eyes used in each experiment, the antibiotics tested, the concentration selected, and the schedule of therapy are listed in Table 4.

RESULTS

Figures 1 to 5 represent the typical corneal lesions which were produced in these experiments. The areas of maximum involvement in the control, as well as the treated, eyes were selected for the high-power magnification. The microscopic slides were stained with hematoxylin and eosin. In Figures 1 and 4 sections for magnification were taken at the point of perforation.

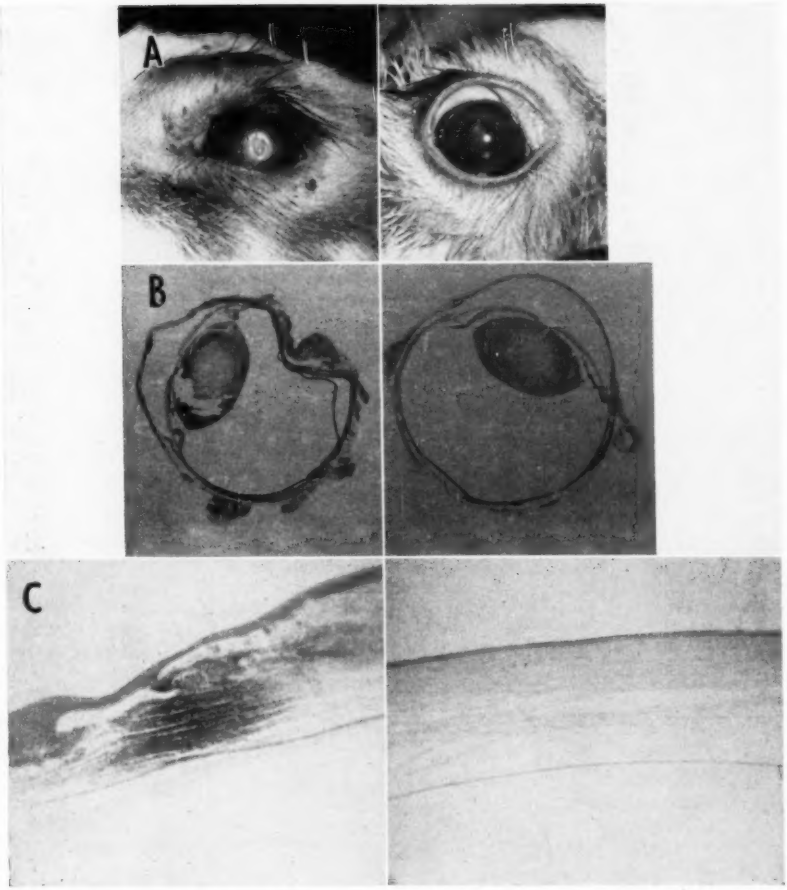

Fig. 3.—Effect of 10 days' treatment with terramycin of rabbit eyes experimentally infected with Escherichia coli.

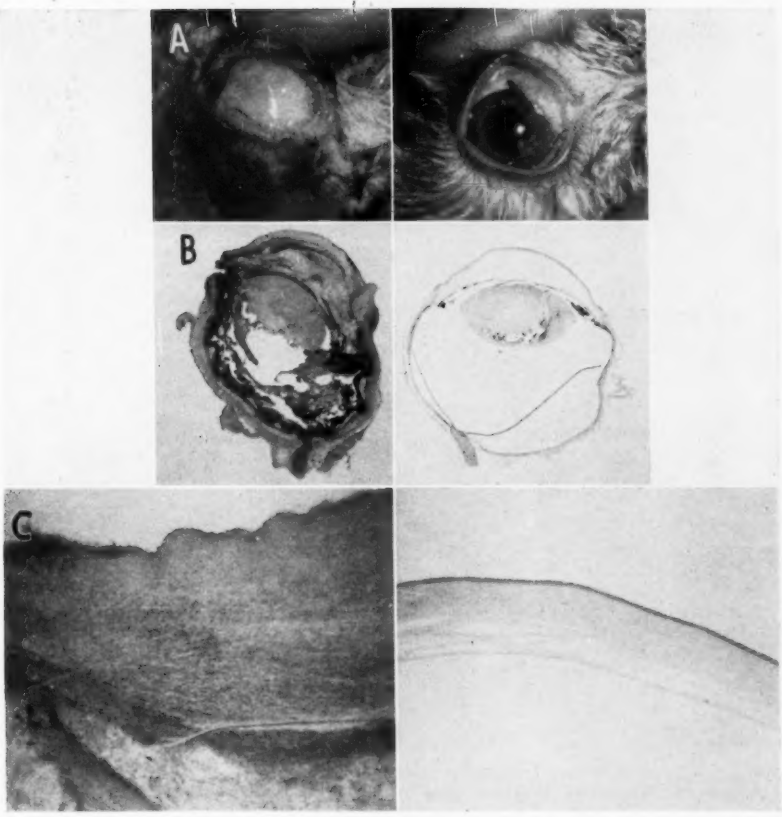

Fig. 4.—Effect of 10 days' treatment with terramycin of rabbit eyes experimentally infected with Diplococcus pneumoniae.

In Figure 6 is presented a statistical comparison of the severity of the lesions produced in the control eyes and that of the lesions in the treated eyes. The comparative effectiveness of the antibiotics employed against these standard lesions is clearly illustrated.

These results emphasize the observations that in vitro sensitivity studies may act as a guide in the selection of antibiotics for therapy, but such selections will

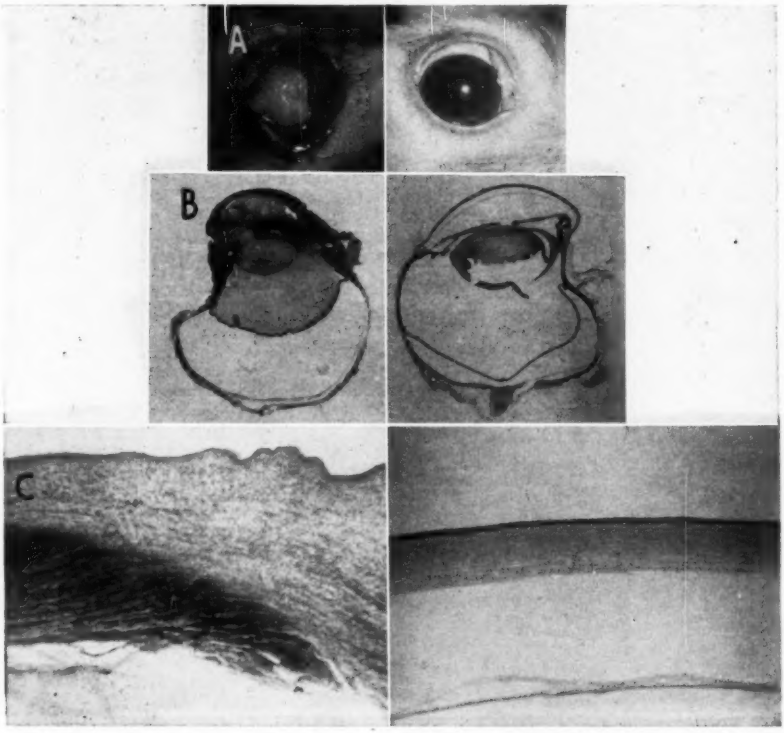

Fig. 5.—Effect of 10 days' treatment with terramycin of rabbit eyes experimentally infected with hemolytic streptococci. Photomicrographs are of eyes enucleated at 60 days.

not be infallible. The final proof rests with clinical trial. Response of one strain of one organism does not mean that all strains will act similarly.

It is evident from these data that terramycin was highly successful against many varieties of organisms tested, and that it compares favorably, for those strains of organisms, with the other antibiotics tested. Neomycin was also impressive, but was not as completely successful as terramycin.

The earlier the therapy was instituted, the better was the result.

Local therapy appears to be an adequate method for therapy of bacterial corneal ulcerations when instituted early.

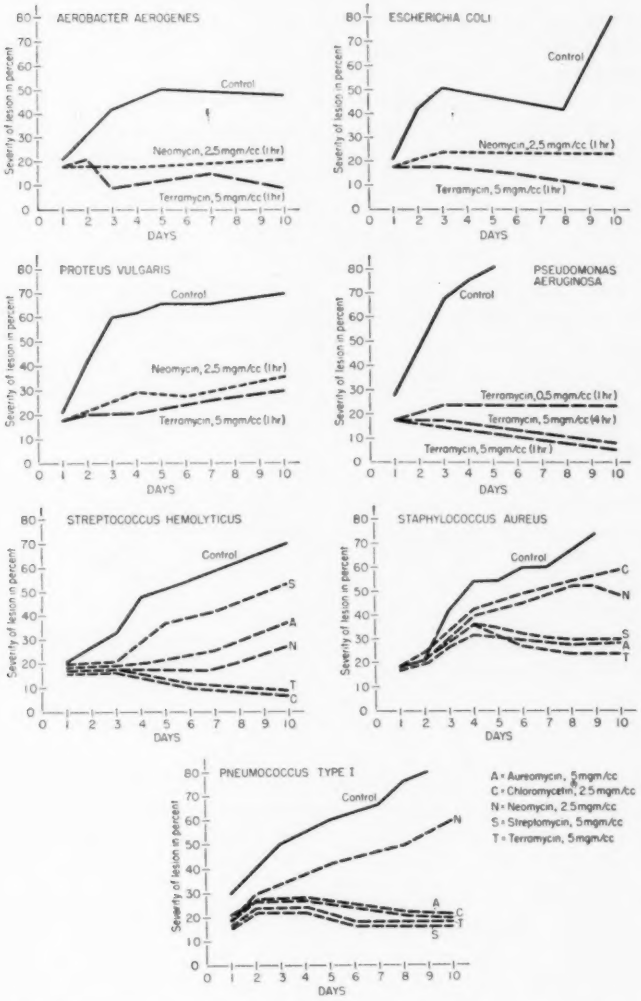

Fig. 6.—Influence of antibiotics in experimental keratitis in the rabbit eye.

COMMENT

The findings in these experiments are in agreement with Robson and Scott's [2c] observations that the experimentally produced lesions vary in severity in different animals, and are essentially the same in the two eyes of any one animal, in the absence of treatment. For that reason the right eye in all experiments was chosen as the treated eye, while the left served as a control. There was a definite correlation between the general health of the rabbits and their response to the experimental corneal lesions.

Many of the strains of Staph. aureus and the hemolytic streptococci employed in these experiments were unable to produce corneal lesions. Through repeated trial intracorneal injections, satisfactory strains of pathogenic staphylococci and streptococci were finally found. Brown and Pugh [2d] had similar difficulty in their attempts to produce standard Staph. aureus lesions of the rabbit cornea.

The percentage of deaths due to pneumococcic septicemia in the experiments with Type 1 D. pneumoniae utilized in this study was much higher than that found by Robson and Scott,[2e] who used a Type 19 Pneumococcus.

Hypopyon was produced readily with either the Streptococcus or the staphylococcus. Unpublished observations of Robson and Scott in 1943 [2e] were that hypopyon did not form as frequently with hemolytic streptococci as it did with Staph. aureus.

The present study bore out the finding of Robson and Scott [2f] that there is a definitely poorer prognosis when initial treatment is instituted in the experimental animals more than one hour after inoculation.

SUMMARY

Terramycin topically applied controlled experimental keratitis due to a variety of Gram-positive, penicillin-resistant, and Gram-negative organisms.

Topical use of neomycin was also of benefit in experimental bacterial keratitis, but was not as completely successful as terramycin.

In vitro studies of bacterial sensitivity to antibiotics were not always confirmed by in vivo trial.

The importance of early treatment of experimental ulcers with an optimal concentration of the antibiotic is demonstrated by the action of various concentrations of terramycin employed at different time intervals following the intracorneal injection of Ps. aeruginosa.

Merck & Company, Inc., supplied the neomycin and streptomycin; Chas. Pfizer & Company, Inc., the terramycin; Lederle Laboratories Division, the aureomycin, and Parke, Davis & Company, the chloramphenicol.

Dr. T. G. Anderson, of Temple University School of Medicine, made the bacteriological studies.

SYMPATHETIC OPHTHALMIA

Similarity to Bilateral Endophthalmitis Phacoanaphylactica; New Therapeutic Methods

GEORGE M. HAIK, M.D.
RICHEY L. WAUGH Jr., M.D.
AND
WOOD LYDA, M.D.
NEW ORLEANS

THERE are certain diseases in all fields of medicine whose essential data have come to be more or less taken for granted. Sympathetic ophthalmia is one of these. Its existence, as Woods [1] pointed out in an excellent review of the whole subject, has been realized for almost a thousand years. Its clinical aspects were very well described more than 100 years ago. The pathologic changes in the exciting eye were set forth in considerable detail almost 50 years ago. The potentially devastating character of the disease is thoroughly appreciated by any ophthalmologist who has ever encountered it in his practice. No really satisfactory treatment for it has ever been devised.

A recent experience of our own, in which the histologic picture was at complete variance with the classic clinical picture of sympathetic ophthalmia which the patient presented, has made us wonder whether it would not be well to examine again certain of the facts of this disease which are now taken for granted. The presentation of that experience and of its clinical implications is our first purpose in this communication. Our second is to report what we have been able to determine concerning the effects of corticotropin and cortisone therapy in sympathetic ophthalmia, as indicated by our own experience and the experiences of 29 other ophthalmologists who have shared their results with us.

HISTOLOGIC PICTURE

The Exciting Eye.—A large enough number of histologic studies have been made on the exciting eye to warrant the full acceptance of E. Fuchs's [2] original observations, which showed that the most important pathologic changes were (1) uniform infiltration, chiefly by lymphocytes, of the tissues about the uveal vessels and emissary veins; (2) occasional absence of the epithelioid and giant cells commonly associated with lymphocytic infiltration; (3) concentration of the infiltration

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From the Division of Ophthalmology, Louisiana State University School of Medicine.

Read before the Section on Ophthalmology at the One-Hundredth Annual Session of the American Medical Association, Atlantic City, N. J., June 15, 1951.

1. Woods, A. C.: Sympathetic Ophthalmia, Am. J. Ophth. **19**:9-16 (Jan.); 100-109 (Feb.) 1936.

2. Fuchs, E.: Über sympathisierende Entzündung (nebst Bermerkungen über seröse traumatische Iritis), von Graefes Arch. Ophth. **61**:365-456, 1905.

in the posterior third of the iris; (4) exudation about the iris and over the anterior surface of the lens; (5) changes in the pigmented epithelium, with sparing of the choriocapillaris, and (6) notable absence of caseation and necrosis.

A number of other observations, some well established and others of yet unknown significance, have since been added to Fuchs's original findings. It is now known that Dalen-Fuchs nodules are not always present in sympathetic ophthalmia and that their presence is not necessarily diagnostic of the disease. When eosinophiles are present, they tend to occur in groups in the choroid. Redslob [3] stated the belief that there is always present a "chancre of inoculation," as he called it, from which the inflammatory process spreads. Samuels [4] emphasized that the basic pathologic process is a uveoscleritis, with further orbital involvement. Friedenwald [5] stressed the phagocytosis of pigment by epithelioid and giant cells. Incarceration of the vitreous in the traumatic or surgical wound may be as important in the development of the disease as the presence of uveal material or, as de Veer [6] believed, of lens material. Several observers have called attention to the remarkable similarity between the histologic picture in sympathetic ophthalmia and the histologic lesions of experimental uveitis produced by sensitization to a variety of agents.[7]

The Sympathizing Eye.—It has been generally accepted, since E. Fuchs [2] published his original description of the histologic picture of the exciting eye in sympathetic ophthalmia, that the changes in the sympathizing eye are essentially similar. In the experience to which we have already referred, however, in which the clinical picture of sympathetic ophthalmia was classic, the deviations from the classic histologic picture were so striking in the sections of the sympathizing eye that we were led to reconsider our traditional concept.

Gross examination of this untraumatized, sympathizing eye revealed an apparently normal lens, with an intact capsule supported by a few zonule fibers. The vitreous was fluid. There was a poorly formed, but definite, membrane on the inner aspect of the retina.

Microscopic examination of the remainder of the eye (Figs. 1 and 2)—unfortunately lacking the lens, which was lost in tissue handling—revealed a disproportionately greater degree of infiltration in the anterior than in the posterior uvea; predominance of plasma cells, with macrophages next in order of frequency; diffuse infiltration of the iris, with no tendency toward posterior localization; marked infiltration of the ciliary body around the major circle of the iris; lymphocytic infiltration of the episcleral tissue around the limbus; absence of Dalen-Fuchs

3. Redslob, E.: Considerations anciennes et nouvelles sur la pathologie et la pathogénie de l'ophtalmie sympathique, Ophthalmologica **118**:483-495 (Oct.-Nov.) 1949.

4. Samuels, B.: Significance of Specific Infiltration at the Site of Injury in Sympathetic Ophthalmia, Arch. Ophth. **9**:540-559 (April) 1933; Sympathetic Scleritis, ibid. **10**:185-197 (Aug.) 1933.

5. Friedenwald, J. S.: Notes on the Allergy Theory of Sympathetic Ophthalmia, Am. J. Ophth. **17**:1008-1018 (Nov.) 1934.

6. de Veer, J. A.: Endophthalmitis Phacoanaphylactica and Its Relation to Sympathetic Ophthalmia, Arch. Ophth. **23**:237-252 (Feb.) 1940.

7. Schlaegel, T. F., Jr., and Davis, J. B.: The Reaction of the Rabbit Eye to Normal Horse Serum: Sensitization by Intradermal Injection, Am. J. Ophth. **26**:785-798 (Aug.) 1943. Collins, R. C.: Experimental Studies on Sympathetic Ophthalmia, ibid. **32**:1687-1699 (Dec.) 1949.

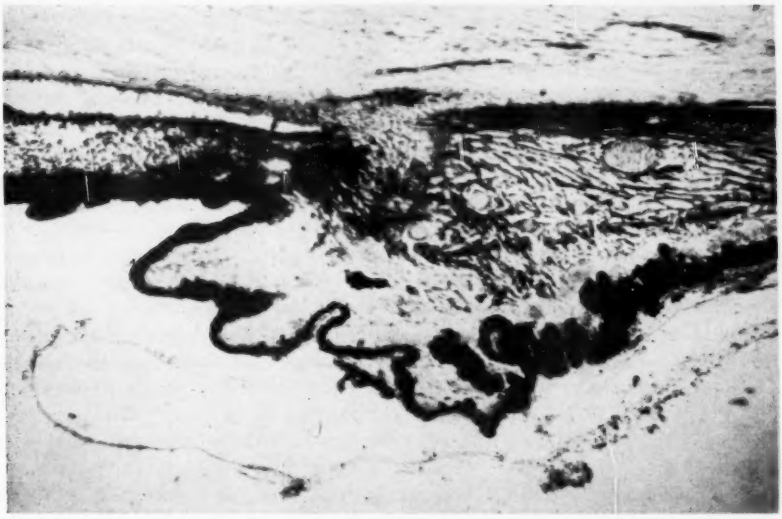

Fig. 1.—Section from root of iris showing iridocyclitis with inflammatory and exudative changes. The patient presented the classic clinical picture of sympathetic ophthalmia.

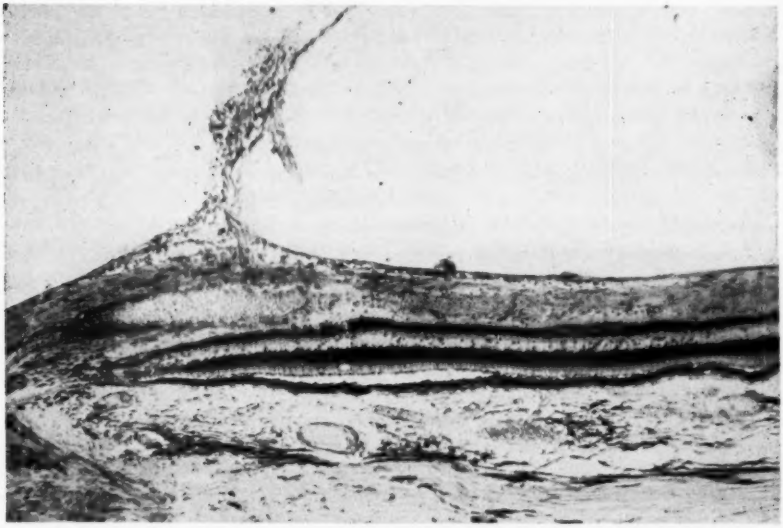

Fig. 2.—Section from posterior uvea of eye shown in Figure 1. Note gliosis of neural elements, membrane formation, and relative sparing of the choroid.

bodies; gliosis of the ganglion-cell layer; retinal perivasculitis; inflammatory membrane formation, with early vascularization, extending from the ciliary body to the optic disk, with the internal limiting membrane practically intact; clumps of mononuclear and polymorphonuclear cells free in the vitreous, and gliosis of the optic nerve with round-cell infiltration of the meningeal spaces.

In the absence of any knowledge of the clinical history of this patient, we should have regarded these findings as indicative of endophthalmitis, a view later shared, in spite of their knowledge of the clinical history, by several ophthalmologists who reviewed the slides for us. The situation was disconcerting. The patient, a 68-year-old diabetic who had been under observation for two years for bilateral immature cataract, had presented the classic clinical picture of sympathetic ophthalmia four weeks after extracapsular cataract extraction, which had been performed when the attempted intracapsular extraction was unsuccessful. The sympathizing eye at this time had an immature cataract. Treatment with a variety of mydriatics was followed by immediate and pronounced sensitization. The disease was severe from the onset and showed no mitigation throughout the year in which the "sympathizing" eye was left *in situ*. It was finally removed because of the development of absolute glaucoma. At the time of writing the "exciting" eye has only light perception.

The discrepancy in this case between the typical clinical picture of sympathetic ophthalmia and the atypical histologic picture prompted us to examine the available literature on the sympathizing eye. We found it surprisingly scanty. Loewenstein,[8] in 1945, collected from the literature the records of 19 examinations, most of them made in Germany before 1900. To these 19 cases he added 4 of his own, and these 4 cases, with 13 cases recorded by Greeves [9] in 1948, constitute, so far as we can determine, the only cases reported in the British literature since his collection was made in which the sympathizing eye was examined. No cases seem to have been recorded in the American literature. Loewenstein, unfortunately, did not list his sources, but priority of publication suggests that the study published by Wood [10] in 1930 is included in his total.

In the 18 sympathizing eyes studied by Loewenstein, Greeves, and Wood, as in our own specimen, the sympathetic disease practically always followed extracapsular extraction of a senile cataract. Furthermore, the composite histologic picture in these eyes, which, like our own, had been removed late in the course of the disease, was strikingly like the picture in our specimen. It included disproportionately greater infiltration of the anterior than of the posterior uvea, a predominance of plasma cells, mononuclear- and polymorphonuclear-cell exudation in the vitreous, and occasional gliosis of the inner portion of the retina.

In five of these eyes, none of which had been subjected to operative intervention, the lens capsule had perforated spontaneously, and infiltration with a variety of inflammatory cells had followed. Only in the case reported by Wood [10] is it known

8. Loewenstein, A.: The Sympathizing Eye, Tr. Ophth. Soc. United Kingdom **65**:219-231, 1945.

9. Greeves, R. A.: A Contribution to the Microscopical Anatomy of the Sympathizing Eye, Brit. J. Ophth. **32**:545-550 (Sept.) 1948.

10. Wood, D. J.: Two Cases of Sympathetic Ophthalmitis, Brit. J. Ophth. **14**:291-297 (June) 1930.

that the second eye also had a mature cataract. Loewenstein and Greeves made no statement concerning the state of the second lens at the time of the original cataract extraction.

We do not propose, of course, on the basis of the study of a single sympathizing eye, to cast aside all the accepted concepts of the histologic changes in sympathetic ophthalmia, even though our own observations are borne out by the few studies of sympathizing eyes recorded in the literature. It seems to us, however, that our experience raises certain questions which must be answered:

1. Is the pathologic process in the sympathizing eye different from that in the exciting eye, as our own and the British cases suggest, or can the deviations from the classic picture observed in these specimens be explained by differences in the duration of the disease? The exciting eye is usually removed early, but the sympathizing eye, if it is removed at all, is usually, as in all of these cases, removed late.

2. Does the apparent deviation from the classic histologic picture observed in our own specimen and those recorded by the British authorities indicate merely a more intensive degree of the same type of tissue reaction present in the exciting eye?

3. Or is it possible that in our own specimen and in some of the specimens described by the British observers the condition is not sympathetic ophthalmia at all, but a fundamentally different disease process? If the latter supposition is sound, two possibilities suggest themselves, endophthalmitis phacoanaphylactica or some other type of bilateral granulomatous uveitis.

Clinical and histologic evidence in these cases suggests that a bilateral form of endophthalmitis phacoanaphylactica has apparently been confused clinically with sympathetic ophthalmia.

Although endophthalmitis phacoanaphylactica is usually considered a unilateral disease, Courtney [11] has shown that a bilateral form exists. In Verhoeff and Lemoine's paper [12] on endophthalmitis phacoanaphylactica, three of their original cases are suggestive of bilateral disease. In seven cases of his own, Courtney recognized a bilateral form of the disease appearing after extracapsular extraction of a senile cataract. In all instances, the second eye had not been traumatized, and the cutaneous sensitivity tests to lens antigen were positive. In one of his cases the microscopic changes were suggestive of endophthalmitis phacoanaphylactica and were associated with spontaneous rupture of the lens capsule. The histologic picture in our case is remarkably similar to that reported by Courtney. By testing with lens antigen, Courtney was able to make a diagnosis of bilateral endophthalmitis phacoanaphylactica in his cases. It is also interesting to note that in our case, as well as in many of those reported by the British, the disease considered to be sympathetic ophthalmia was early in onset, whereas in those of Courtney the onset was later.

In cases of bilateral granulomatous uveitis following extracapsular extraction, and with an onset and appearance characteristic of sympathetic ophthalmia, an early differentiation of bilateral endophthalmitis phacoanaphylactica and sympa-

11. Courtney, R. H.: Endophthalmitis with Secondary Glaucoma Accompanying Absorption of the Crystalline Lens, Tr. Am. Ophth. Soc. **40**:355-369, 1942.

12. Verhoeff, F. H., and Lemoine, A. N.: Endophthalmitis Phacoanaphylactica, Am. J. Ophth. **5**:737 (Sept.) 1922.

thetic ophthalmia is imperative. One of the main means of differentiation may be simultaneous cutaneous sensitivity testing with lens antigen and uveal tissue. Systemic manifestations occasionally seen early in sympathetic ophthalmia may be another means of differentiation.

With an early diagnosis of bilateral endophthalmitis phacoanaphylactica, a different type of therapy would be indicated than if the disease were sympathetic ophthalmia. In mild cases in which corticotropin and cortisone may block the inflammatory reaction, surgical removal of the remaining lens material may be necessary to eliminate the primary focus of anaphylactic disease. In those cases of severe inflammatory reaction in which the lens of the second eye is acting as a secondary focus of anaphylactic disease, a more severely involved second lens may be removed. Removal of the lens in the second eye to control the endophthalmitis and its complications was Courtney's method of control.

SYSTEMIC MANIFESTATIONS

Systemic symptoms and signs may be among the clinical manifestations.[13] Headache, deafness, pigmentary changes, and pleocytosis have now been reported in enough instances, and by sufficiently reliable authorities, to establish their possible association with sympathetic ophthalmia and to suggest that it is a more extensive disease than it is usually considered to be. The electroencephalographic changes reported by Rohmer and Lobstein[14] confirm the impression that a mild meningoencephalitis may occur in some cases, while parallel observations on the Vogt-Koyanagi syndrome[15] make one wonder whether an etiologic relation of this condition to sympathetic ophthalmia may not reasonably be postulated.

We have observed one patient who presented an increased number of lymphocytes in the spinal fluid, though inoculation of the fluid into a chick embryo produced no growth. It is perhaps significant that this observation was made the day after ocular symptoms first appeared and that the onset of symptoms was associated with a severe headache. If we had repeated the examination, we suspect that we might not have been able to repeat the observation. This has been the experience of other observers. It might well be that if patients with sympathetic ophthalmia were studied more thoroughly in the early stages of the disease, more such observations would be recorded, and, conceivably, the virus which has been postulated as the cause of the disease might be identified, as it has been under the same circumstances in other virus diseases.

CORTICOTROPIN AND CORTISONE THERAPY

It is hardly necessary to say that evaluation of therapy in sympathetic ophthalmia is difficult, as it is in any disease which varies from patient to patient and which tends to natural remissions. Improvement has been reported with methods of treatment which could not possibly have any effect on the disease. Variations in the disease process serve to explain why some patients do well with types of

13. Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947.

14. Rohmer, F., and Lobstein, A.: Bearing of Electro-Encephalography on Some Ocular Diseases, Especially Sympathetic Ophthalmia, Rev. neurol. **82**:571-573, 1950; abstracted in Ophth. Lit. **4**:607 (March) 1951.

15. Cowper, A. R.: Harada's Disease and Vogt-Koyanagi Syndrome: Uveoencephalitis, A. M. A. Arch. Ophth. **45**:367-376 (April) 1951.

treatment under which others show progressive deterioration. Furthermore, as Woods [1] pointed out in 1936, the duration of the disease must always be taken into consideration in an analysis of results: Any method of treatment which is at all effective is most effective when it is instituted early.

The introduction of cortisone and corticotropin has opened new therapeutic vistas in ocular disease, as in many other branches of medicine. Woods and Wood [16] have shown experimentally that these hormonal agents act locally to block the inflammatory and exudative response of ocular tissues to a variety of irritative and hypersensitive reactions, with effects varying from temporary and partial to complete and apparently permanent, and also varying in relation to the dosage and the duration of treatment. A particularly significant part of their investigations was the demonstration that while granulomatous lesions can progress under corticotropin and cortisone therapy without manifestations of inflammation or exudation, both inflammation and exudation will recur if the stimulus is permitted to persist after therapy is withdrawn. Under controlled ophthalmic conditions, Woods and Wood thus confirmed Hench's [17] thesis that these hormones, in spite of their clinical effectiveness, do not really cure anything at all. Still another part of their investigation which should not be overlooked is their demonstration that corticotropin and cortisone sometimes affect certain granulomatous diseases adversely.

Of 58 ophthalmologists [18] who replied to our inquiries about their experiences with corticotropin and cortisone in sympathetic ophthalmia, 29 replied that they had had no patients with this complication since these agents became available. With care to exclude those patients who might have shown clinical endophthalmitis phacoanaphylactica, the remaining 29 ophthalmologists carried out treatment in a total of 69 apparent cases of sympathetic ophthalmia. These, plus 3 cases of our own and 8 cases already recorded in the literature,[19] make a total, with all dupli-

16. (*a*) Woods, A. C.: Clinical and Experimental Observation on the Use of ACTH and Cortisone in Ocular Inflammatory Disease, Am. J. Ophth. **33**:1325-1349 (Sept.) 1950; (*b*) Present Status of ACTH and Cortisone in Ophthalmology (Gifford Memorial Lecture), to be published. (*c*) Woods, A. C., and Woods, R. M.: Action of ACTH and Cortisone on Experimental Ocular Inflammation, Bull. Johns Hopkins Hosp. **87**:482-504 (Nov.) 1950.

17. Hench, P. S.: Introduction: Cortisone and ACTH in Clinical Medicine, Proc. Staff Meet., Mayo Clin. **25**:474-476 (Aug. 16) 1950.

18. The following ophthalmologists furnished the data upon which this study is based:

Drs. S. D. Aiken; F. H. Adler; B. Y. Alvis; C. Berens; M. L. Berliner; F. P. Calhoun; A. Callahan; R. Castroviejo; F. C. Cordes; T. O Coston; R. K. Daily; A. G. DeVoe; J. H. Dunnington; E. B. Dunphy; A. J. Elliot; H. Gifford; J. S. Friedenwald; E. L. Goar; T. Gundersen; P. Heath; M. J. Hogan; F. Hollabaugh; W. F. Hughes, Jr.; C. E. Iliff; C. D. F. Jensen; L. V. Johnson; H. M. Katzin; P. C. Kronfeld; S. R. Irvine; J. Laval; A. N. Lemoine; I. H. Leopold; D. J. Lyle; R. J. Masters; P. R. McDonald; J. S. McGavic; J. W. McKinney; J. M. McLean; S. D. McPherson Jr.; F. H. Newton; W. C. Owens; R. T. Paton; B. F. Payne; D. K. Pischel; M. H. Post Jr.; A. B. Reese; C. W. Rucker; B. Samuels; H. G. Scheie; C. P. Sullivan; T. E. Sanders; M. Thomas; H. E. Thorpe; P. Thygeson; S. M. Truhlsen; D. Vail; L. von Sallmann; K. C. Swan, and A. C. Woods.

19. (*a*) Woods.[16a] (*b*) Fitzgerald, J. R.; Bellows, J. G.; Donegan, J. M.; Gamble, R. C.; Krause, A. C.; Mann, W. A.; Pearlman, M. D., and Zekman, T. N.: Early Clinical Results of ACTH and Cortisone Treatment of Ocular Diseases, A. M. A. Arch. Ophth. **45**:320-333 (March) 1951. (*c*) Leopold, I. H.: Clinical Trial with Chloramphenicol in Ocular Infections, ibid. **45**:33-52 (Jan.) 1951. (*d*) Raiford, M.: Use of Cortisone and ACTH in Ophthalmology, Guildcraft **25**:15-19, 22-24 (April) 1951.

cations omitted, of 80 cases of sympathetic ophthalmia in which hormone therapy was given. In 72 of these, sufficient data are available for a statement of results (Fig. 3).

In the interpretation of these results, two points must, of course, be borne in mind. The first is that corticotropin and cortisone have been available for too brief a period to permit anyone to speak of cures; most of the results reported to us, in fact, occurred, like our own, in very recent cases. The second point to be remembered is that there is always a wide variability of opinion as to what constitutes a good result. We have no doubt that many observers have classified mere

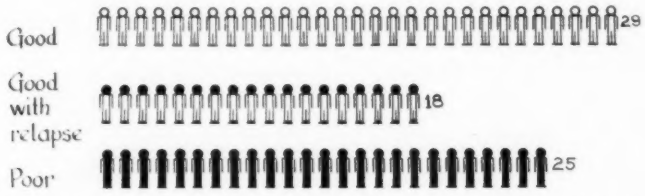

Fig. 3.—Results of cortisone and corticotropin therapy in 72 collected cases of sympathetic ophthalmia.

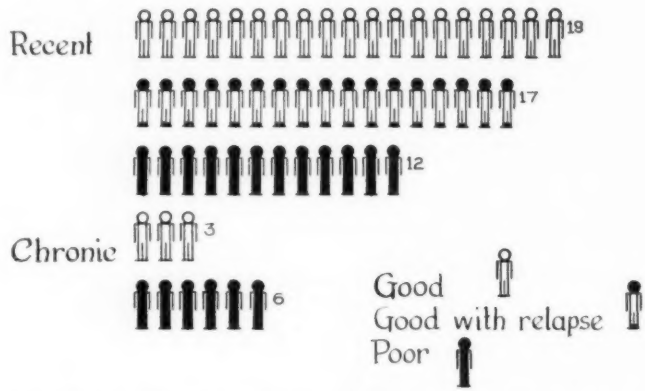

Fig. 4.—Results of cortisone and corticotropin therapy in 57 collected cases of sympathetic ophthalmia in which classification was possible according to duration.

arrest of the process as a favorable outcome, as indeed it is. When, with these reservations, the stated results and the comments of the ophthalmologists who cared for the 72 patients are taken into consideration, the following tentative conclusions seem warranted:

1. Corticotropin and cortisone seem able to control the inflammatory and exudative processes in some, but in by no means all, cases of sympathetic ophthalmia.

2. These agents are more likely to accomplish the desired results if they are given early in the course of the disease (Fig. 4) and if they are given in sufficiently large doses.

3. They are also more likely to be effective in mild than in severe sympathetic ophthalmia (Fig. 5).

4. Inflammatory and exudative processes tend to clear, sometimes suddenly and dramatically, within a few days after therapy has been instituted.

5. Relapses seem likely to occur if therapy is withdrawn, or if the dose is decreased, too soon after treatment has been instituted, though the optimum dosage and duration of treatment remain to be determined.

6. If results in this series of cases can be taken at their face value, re-treatment after relapse is likely to be successful. Second courses of therapy were given in 17 of the 18 cases in which relapse had occurred and were successful in controlling the sympathetic disease in 16 of the 17 cases.

7. The wide variety of dosages and routes of administration employed in this series defies tabulation and suggests that therapeutic methods are still in process of determination. Systemic administration seems advisable in the acute stage of

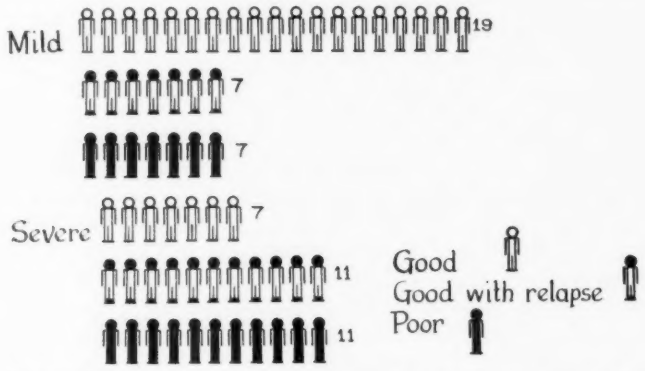

Fig. 5.—Results of cortisone and corticotropin therapy in 62 collected cases of sympathetic ophthalmia in which classification was possible according to severity.

sympathetic ophthalmia, and topical administration can apparently be relied upon to prevent recurrence once control has been accomplished. It was noted in some cases in this series that systemic administration of both corticotropin and cortisone produced good results after topical administration, which had been employed initially, had been unsuccessful.

8. It is difficult to determine from this series whether or not secondary glaucoma can be prevented by corticotropin and cortisone. This sequela of sympathetic ophthalmia was specifically mentioned in only 7 of the 25 unsuccessful cases, but since complete details were lacking in a large number of the other cases, it cannot be assumed that the specified cases represent the real incidence of secondary glaucoma. In two of the seven cases cortisone therapy brought the disease under control.

9. Intraocular procedures can apparently be carried out, under the protection of corticotropin or cortisone, without fear of a flare-up of the sympathizing disease. Three of the ophthalmologists who replied to our inquiries reported such results.

Gundersen [18] performed an iridectomy for glaucoma; Thorpe,[18] a cataract extraction, and McLean,[18] an iridectomy and a cataract extraction. Our own experience with three operations in two patients has been equally satisfactory. One of these patients was submitted to an iridencleisis and later to a cataract extraction. The history of the other patient seems worth recording in detail.

The patient, a white man aged 70, had a stormy recovery after an unsuccessful intracapsular cataract extraction on the right eye and still had a somewhat active uveitis on this side when he left the hospital, 10 days after operation. The left eye, on repeated examinations for two months before operation and on daily examinations after operation, was entirely free from disease. The patient was seen almost daily after he left the hospital and for nine weeks remained in the same condition. Then, practically overnight, a typical clinical picture of sympathetic ophthalmia developed. Severe headache was a prominent symptom. Examination of the spinal fluid revealed pleocytosis. Cortisone therapy was begun immediately, systemically and topically. Forty-eight hours after the appearance of the sympathizing disease the lens cortex remaining in the eye was removed, on the basis of Redslob's [3] theory that sympathetic ophthalmia arises from a "chancre of inoculation." It took considerable courage, we must admit, to undertake the secondary operation so soon after the onset of the acute episode, but the rationale of the procedure is clear, and the smooth recovery and favorable outcome have made us feel that under similar cortisone protection any indicated procedure may be undertaken on the exciting eye without long delay and with good prospects of success. It also seems to us that whenever an inflammatory focus exists in a surgically treated or an injured eye, its surgical removal might well be considered a prophylactic measure, before sympathetic ophthalmia has developed.

Theoretically, the use of corticotropin and cortisone before and immediately after operation is undesirable, because these agents are believed to retard wound healing. On the other hand, the clinical experience related, although limited to six operations, suggests that the theoretical risk is justified in view of the advantages of suppressing inflammation and exudation by the use of these new agents. The risk can be partly overcome by leaving the sutures in place for a longer time than usual.

10. That one should constantly bear in mind the dangers of systemic administration of corticotropin and cortisone over long periods is shown by the death from cardiac disease, precipitated by the use of these agents, which occurred in one of the cases reported to us, as well as by the transient period of disorientation experienced by one of our own patients while under systemic cortisone therapy.

Adjunct Therapy.—Even when corticotropin and cortisone are used, prompt mydriasis is still an essential part of the treatment of sympathetic ophthalmia, just as it is of any other uveitis. Experience suggests that the topical use of cortisone, in addition to its effect on inflammation and exudation, may lessen the chances of sensitization to mydriatics, which is peculiarly likely to occur in this disease, and to better the prospects for control if it should occur.

The use of corticotropin and cortisone does not eliminate the need for antibiotic therapy. If anything, it increases the necessity for its employment, since these agents may suppress the manifestations of an infection which continues to exist.

Chloramphenicol (chloromycetin®) is often an excellent choice because of its superior penetrating power.[19a]

Foreign protein therapy has been widely used in sympathetic ophthalmia, for both prophylactic and therapeutic purposes, but entirely on an empiric basis. Formerly the reaction was thought to be anamnestic. Since 1946, however, when Selye [20] advanced the concept of the general adaptation syndrome, it has been thought that the foreign protein serves as an alarm stimulus that brings about a liberation of an adrenocorticotropic hormone from the pituitary gland. Recently Arendshorst and Falls,[21] by means of the Thorn test, have shown that this is exactly what happens when typhoid H antigen is used in ocular disease. The inference, therefore, seems justified that in the past physicians have apparently, if unwittingly, been providing their patients with an increased amount of circulating corticotropin whenever they have used foreign protein therapy. This theory would explain why Woods,[1] for instance, in his analysis of the therapy of sympathetic ophthalmia, concluded that when the reported cases were analyzed from the standpoint of duration, the best results were accomplished with the Verhoeff-Irvine treatment with diphtheria antitoxin.

SUMMARY AND CONCLUSIONS

Personal experience in a clear-cut clinical case of sympathetic ophthalmia following intracapsular cataract extraction, in which the histologic picture in the sympathizing eye was indicative of endophthalmitis, led to a review of the literature and to the finding of 18 other cases, all in the British literature, in which a similar discrepancy existed. It was eventually concluded that clinical sympathetic ophthalmia is not always what it seems and that in some cases, at least, the disease which is present may be a bilateral form of endophthalmitis phacoanaphylactica.

The implications of this possible diagnostic error are explored. If the assumption is correct that apparent sympathetic ophthalmia is sometimes not that disease, but a bilateral form of endophthalmitis phacoanaphylactica, a reexamination of therapeutic practices is indicated. Enucleation may not be as imperative as some observers believe it to be. Instead, the proper procedure would seem to be removal of any lens material remaining in an eye operated upon, on the ground that it is the primary focus of the anaphylactic disease, or, if indications exist, removal of the lens in the other eye, on the ground that it may be the secondary focus.

The present status of corticotropin and cortisone is evaluated on the basis of 69 collected cases and 3 personally observed cases. These agents seem capable of controlling the inflammatory and exudative processes in some cases of the disease, especially if they are given early and if the disease is mild. Relapse may occur if therapy is withdrawn too soon or if too small a dose is used, though re-treatment seems remarkably successful. The pattern of dosage and the best routes of administration are not yet established. It is impossible to determine from this series whether or not secondary glaucoma can be prevented by this type of hormonal therapy.

19a. Leopold, I. H.: Clinical Trial with Chloramphenicol in Ocular Infections, A. M. A. Arch. Ophth. **45**:44-52 (Jan.) 1951.

20. Selye, H.: General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**:117-230 (Feb.) 1946.

21. Arendshorst, W., and Falls, H. F.: Role of the Adrenal Cortex in Treatment of Ocular Diseases with Pyrogenic Substances, Arch. Ophth. **44**:635-642 (Nov.) 1950.

Results in six operations, three of them performed personally, suggest that under cortisone protection surgical treatment can safely be undertaken in sympathetic ophthalmia, often quite promptly, with good results and without fear of the consequences which once would have followed such a course.

Results in a personal case, in which operation was carried out uneventfully and with good results under cortisone protection, suggest that it might be wise in any case in which an inflammatory focus (Redslob's "chancre of inoculation") exists after operation to remove it promptly, as a prophylactic measure, or, if sympathetic ophthalmia has already developed, as a therapeutic measure.

The availability of corticotropin and cortisone does not lessen the need for, or the usefulness of, mydriatic, antibiotic, and foreign protein therapy as adjunct prophylactic or therapeutic measures. The recent discovery that foreign protein therapy is really an indirect form of corticotropin therapy clarifies the hitherto unexplained good results accomplished by this form of treatment.

ABSTRACT OF DISCUSSION

Dr. Alan C. Woods, Baltimore: This well-written paper by Dr. Haik and his associates immediately raises several interesting questions. The first is whether uveal inflammation following an extracapsular extraction in the fellow eye is always to be regarded as sympathetic ophthalmia or whether it may not, in fact, be another disease entity. In this paper Dr. Haik has reported a case of delayed uveitis complicated by absolute glaucoma which followed an extracapsular extraction in the fellow eye. The histologic picture in the supposed "sympathizing" eye was characterized by the presence of macrophages and plasma cells, chiefly in the anterior segment, together with membrane formation—a picture suggestive of endophthalmitis phacoanaphylactica, and not sympathetic ophthalmia. He advances the hypothesis that the underlying mechanism in this case may not be that of sympathetic ophthalmia but may be related to a hypersensitivity to lens protein which developed as a result of the extracapsular extraction. This reasoning is sound, and, as Dr. Haik states in his paper, is a restatement and an extension of a similar hypothesis advanced by Dr. Courtney in 1942. It will be recalled that Dr. Courtney reported seven cases, all quite similar to the one reported by Dr. Haik. In all seven cases there had been an extracapsular extraction in the fellow eye. In all cases there was delayed uveitis in the second eye, and in five cases, secondary glaucoma. In all seven cases there was a pronounced cutaneous hypersensitivity to lens protein, demonstrated by intracutaneous testing. In one case the second eye was involved and was removed, and the histologic picture was almost identical with that reported by Dr. Haik—macrophages, lymphocyte and plasma-cell infiltration, and membrane formation on lamina elastica posterior (Descemet's membrane), the pathologic changes being chiefly in the anterior ocular segment.

I believe that Dr. Courtney's and Dr. Haik's reasoning is sound. Once hypersensitivity to the organic specific lens protein is established as the result of the absorption of lens protein, the absorption of lens protein by the second eye could theoretically produce a local inflammatory reaction. Whether such absorption in the second eye results from a small spontaneous rupture of the lens capsule or from absorption of lens protein through a damaged or weakened capsule is an academic question. There is also the academic question whether added absorption of bacterial toxins, from a "primary chancre" or from a remote focus of infection, is necessary to produce the original sensitization and the later intoxication in the second eye. Lens protein is a notoriously weak antigen, and its antigenic activity may be greatly enhanced by the addition of nonspecific bacterial antigens—the synergistic action of antigens first demonstrated by the late Dr. E. L. Burky. There is also the more remote possibility that the uveitis in the second eye is related to a

possible inherent toxicity of lens protein—a lens-induced uveitis. This explanation is, however, more plausible when applied to the uveitis in the "exciting" eye. In the second eye I should suspect the allergic type of reaction.

If one accepts either of these hypotheses, i. e., that the delayed uveitis and secondary glaucoma in the second eye are due to sensitization and intoxication by lens protein or to the absorption of toxic lens material, the therapeutic conclusions suggested by Dr. Haik logically follow. In such cases of delayed uveitis the possibility of a hypersensitivity to lens protein should first be explored, and if such a hypersensitivity is found, desensitization of the patient with a mixture of lens protein and Staphylococcus toxin is in order. If the patient is insensitive to lens protein and the clinical picture is not that of sympathetic ophthalmia, a lens-induced uveitis should be considered and the lens or remaining lens material be duly removed. I have certainly seen cases which superficially suggest sympathetic ophthalmia but which on study appear to fall into one of these two groups. I have not as yet had the opportunity for a histologic examination of the second eye.

The latter part of Dr. Haik's paper is a most valuable summary of the general over-all effects of adrenocorticotropic hormone therapy in sympathetic ophthalmia. As is usually the case with statistics gathered by questionnaire, the results scarcely lend themselves to exact analysis—i. e., to a study of the relative effects of cortisone and corticotropin therapy, of parenteral and topical administration, of intravenous and intramuscular use of corticotropin; of the relation of the local therapeutic result to the eosinophile response; of the relation of duration and intensity of treatment to the therapeutic result, etc. All these factors would weigh heavily in the evaluation of the results. Especially interesting would be an analysis of the failures—did the failure rate parallel a lack of response in the eosinophile count? Was intravenous administration of corticotropin used in the cases in which no response was observed by intramuscular injection of the hormone? We have recently seen several cases of ocular disease in which brilliant therapeutic results followed intravenous use of corticotropin after intramuscular injection had been inefficacious, the apparent reason being the local destruction of the intramuscularly administered corticotropin by the proteolytic muscle ferments.

Yet, despite these defects, which undoubtedly are inherent in the method of attack and are beyond Dr. Haik's control, the over-all results of his study are striking. Of 72 patients with sympathetic ophthalmia, without regard to duration or severity of the disease, an immediate favorable result was observed in 47, or 64%, although 18, or approximately 40%, of these later had a relapse, the relapse usually being controlled by further therapy. This is a definitely higher percentage of favorable results than that obtained by any other method of treatment. When the results are analyzed according to duration and severity of the disease, the figures are more striking, favorable results being obtained in approximately 75 to 80% of all early and mild cases. It is a reasonable supposition that had therapy been more intense in the cases of failure, or had corticotropin been given intravenously, the percentage of success in the early and mild cases might have been much higher. In late cases, in which organic changes predominate and the usual vicious cycle of the disease has been established, favorable results, in the sense of preservation of vision and prevention of phthisis bulbi, could not be expected.

Dr. Haik's broad conclusions as to the efficacy of this hormone therapy appear fully justified by the statistics submitted. These conclusions are in accord with the experience of other investigators in this field. Corticotropin and cortisone, properly administered, have a profound effect on controlling the exudative and inflammatory phases of many ocular diseases. In essentially self-limited diseases, this early control of exudation and inflammation may simulate a cure, in the sense that the subjective and objective symptoms of the disease are controlled for a period sufficiently long for the disease process to exhaust itself. Sympathetic ophthalmia, whatever may be its cause, is essentially a self-limited disease. It may run a course of several months or several years, but ultimately it burns itself out. Sympathetic ophthalmia

destroys vision for the reason that the inflammatory and exudative phases of the disease produce organic changes in the eye which destroy it functionally. If the inflammatory and exudative phases are controlled by corticotropin or cortisone until the disease process is brought under control by the natural factors of resistance, vision may be preserved. Thus, these agents obviously have their greatest usefulness in early and mild cases of sympathetic ophthalmia, as attested by Dr. Haik's figures. But the beneficial action in these cases should in no way be regarded as a "cure" of sympathetic ophthalmia. All the evidence at hand on the action of these agents supports the statement made in Dr. Haik's paper, i. e., that "corticotropin and cortisone do not cure anything."

In granulomatous diseases which are not self-limited—notably in tuberculosis and syphilis—these agents may temporarily control the exudative and inflammatory character of the lesions, and so radically alter the natural pattern of the disease. Rapidly accumulating evidence indicates, however, that in such infections this alteration in the fundamental pathogenesis of the disease may ultimately prove disastrous, greatly increasing the ultimate extent and severity of the lesions. Thus, while the present evidence is that corticotropin and cortisone are indicated in the treatment of sympathetic ophthalmia and other self-limited inflammatory ocular diseases, they should not be employed in progressive granulomatous infections, in which they apparently inhibit fibrosis and encapsulation of the lesions and so destroy the natural mechanism of the body against such diseases.

DR. PAUL A. CHANDLER, Boston: Dr. Haik and his associates have presented the pathologic changes in the sympathizing eye in a case of supposed sympathetic disease which followed extracapsular cataract extraction in the other eye and have reviewed the literature concerning similar cases. They believe that the pathologic picture in their own case and in some of the cases from the literature more closely resembles endophthalmitis phacoanaphylactica than true sympathetic ophthalmia, and they have discussed the clinical implications of this observation. The latter part of the paper is concerned with the treatment of sympathetic ophthalmia with corticotropin and cortisone.

The term endophthalmitis phacoanaphylactica is used only in pathologic diagnosis and implies a purely allergic phenomenon. As I understand it, the most characteristic pathologic feature is the invasion of the lens by polymorphonuclear leucocytes and endothelial phagocytes. "Lens reaction" is the term most commonly employed clinically and may include toxic, as well as allergic, reactions.

Unilateral lens reaction is a fairly common disease. One sees it after perforating wounds of the lens, after extracapsular cataract extraction, and not infrequently in cases of hypermature cataract in which there has presumably been spontaneous rupture of the posterior capsule or leakage of lens protein through a thinned posterior capsule. In cases of the last type acute glaucoma is the rule, and the whole condition is relieved by extraction of the lens. In the other instances the condition clears up after removal or absorption of the remaining lens cortex.

Why are unilateral cases so common and the bilateral ones so rare? Is the state of the lens in the sympathizing eye a factor? In five of the cases reported from the literature, pathologic examination revealed rupture of the lens capsule; presumably, therefore, a hypermature cataract was present in these cases. Must there be a mature or a hypermature cataract in the sympathizing eye to produce the syndrome described? If this is true, then the "sympathizing" eye in an obviously allergic person has every reason to show evidences of lens reaction on its own. If, on the other hand, the fellow eye in such cases can become involved, even if the lens is clear or only an incipient or immature cataract is present, the problem of clinical differentiation from true sympathetic ophthalmia will be most difficult.

I have observed cases of bilateral uveitis after extracapsular cataract extraction on one eye, with a hypermature cataract in the fellow eye, in which the condition cleared up in the eye operated on when the lens cortex was absorbed and in the fellow eye after extraction of the lens. The disease was not considered sympathetic

and was treated accordingly. In these eyes none of the usual causes of sympathetic disease, such as incarceration of the iris or prolapse of iris, was present.

In other cases of bilateral uveitis after extracapsular cataract extraction in one eye, in which one of the latter conditions was present in the first eye, intracapsular extraction of a hypermature cataract in the fellow eye has led to phthisis bulbi, and pathologic examination of the piece of iris removed at operation has revealed evidences of true sympathetic disease. This, of course, was before the days of corticotropin and cortisone. Even with these agents available, however, one would be somewhat reluctant to remove the lens in the sympathizing eye during the active stage of the disease if the condition were true sympathetic ophthalmia, whereas there would be every reason to do so if the condition were due to lens reaction.

How, then, can one make the differential diagnosis? Removal of the exciting eye is certainly not justified as a routine procedure unless the eye is hopelessly blind, first, because the possible beneficial effect on the sympathizing eye is debatable, and second, because in some cases the exciting eye turns out to be the better eye in the end. Perhaps the presence of incarcerated or prolapsed iris in the first eye may give a clue. If bilateral uveitis, due to lens reaction, occurs solely or chiefly in cases in which the lens in the fellow eye is mature or hypermature, this fact would be most helpful in making a clinical diagnosis and arriving at the proper treatment. In the uveitis of lens reaction the corneal precipitates are often large and confluent—more so than in sympathetic disease—but this is not an infallible guide in differential diagnosis. If the uveitis clears up in the first eye when the lens cortex is absorbed, while remaining active in the fellow eye, a diagnosis of true sympathetic ophthalmia would be unlikely, since in the latter condition the inflammation usually waxes and wanes simultaneously in the two eyes. In doubtful cases a skin test for sensitivity to lens protein should prove helpful.

Dr. Haik and his associates have performed a real service in calling attention to the fact that bilateral uveitis following extracapsular cataract extraction on one eye may sometimes be a manifestation of lens reaction, and in pointing out that the treatment of such a condition should be entirely different from that of true sympathetic ophthalmia. The problem of differentiating clinically the two conditions is, it seems to me, a very difficult one.

Dr. S. Rodman Irvine, Baltimore: The authors report an instance of sympathetic ophthalmia, clinically typical, but in which pathologic examination of the sympathizing eye showed nongranulomatous inflammation of the anterior uvea, inconsistent with the classic picture of sympathetic infiltration of uveal tract. They cite cases reported in the literature in which the pathologic picture in the sympathizing eye resembled that in their case, and they propose that the general consensus that the pathologic picture is identical in the two eyes is perhaps erroneous. As an alternative explanation of their findings, they suggest that the case they report may be endophthalmitis phacoanaphylactica, and not sympathetic ophthalmia, and they consider the possibility and necessity of differentiating these two entities, one of which is made worse, and the other cured, by surgical removal of the offending lens. I do not believe that their case, or those cited in the literature, indicate that in sympathetic ophthalmia the pathologic picture differs in the sympathizing eye from that in the activating eye.

Having received this paper well in advance, I had the opportunity of reviewing the material from sympathizing eyes available at the pathology laboratory of the Wilmer Institute. I found one typical case of the disease, with bilateral enucleation, the activating (right) eye having been removed in 1937 and the sympathizing (left) eye in 1940. The specific infiltrate was typical and severe in the right eye and more or less burned out in the sympathizing eye, but there still was apparent slight lymphocytic infiltration of the external layers of the choroid, with rare typical foci of epithelioid cells and slight evidence of pigment phagocytosis. There were three iris specimens from sympathizing eyes in cases with pathologic proof of the disease in the activating eye. All these showed the specific infiltration of lymphocytes and

epithelioid cells, particularly adjacent to the pigment epithelium—the classic picture of sympathetic ophthalmia involving the iris. In the 37 cases of proved sympathetic ophthalmia which I reported in 1940 there was 1 case of typical infiltration of the iris of the sympathizing eye, as judged by microscopic examination. In A. Fuchs's "Atlas of Histopathology of the Eye" (Leipzig, F. Deuticke, 1924) there is a beautiful illustration of the typical disease in a sympathizing eye.

In my opinion, therefore, the evidence supports the belief that the pathologic picture is the same in the two eyes. The condition may differ in degree in the two eyes. Then, too, it is possible that in an eye with hypermature cataract the lens reaction is superimposed on sympathetic ophthalmia.

Verhoeff described the pathologic picture of so-called phacoanaphylaxis consisting of infiltration of tissues about the lens and the lens itself with a combination of polymorphonuclear and giant cells, and characteristically lacking in nodules of epithelioid cells. The reaction, therefore, was not a typical granulomatous infiltrate. In addition, he described a reaction caused by material from a hypermature lens, different from phacoanaphylaxis, and characterized by infiltration of the anterior uvea primarily with lymphocytes, plasma cells, and occasional eosinophiles and by phagocytosis of lens substance which had escaped through the lens capsule into the ocular cavities. This picture is seen clinically as a spontaneous uveitis of rather abrupt onset in a patient with a hypermature lens. In exceptional cases large keratic precipitates develop, and often particulate matter can be seen in the aqueous.

In the picture of phacoanaphylaxis the uveitis is secondary to lens material left in the eye from injury or operation, this lens material being different from the liquefied fluid from a hypermature Morgagnian cataract. There are other reactions to lens material, and all of these might be included under the title "Lens-Induced Uveitis and Glaucoma." A year ago, before the Western Section of the Association for Research, I reported 21 such cases and suggested the following diagnostic points differentiating lens-induced uveitis and sympathetic ophthalmia.

1. Exacerbations of inflammation in sympathetic ophthalmia almost invariably involve the two eyes simultaneously, whereas lens-induced uveitis usually involves one eye only. For instance, uveitis developing subsequent to operation on the opposite eye is probably not sympathetic uveitis unless the presumed activating eye is also inflamed.

2. The aqueous in lens-induced uveitis often shows particulate matter, a proportionately high amount of protein that does not clot, and few cells, as compared with the aqueous from a case of equally severe uveitis of other origin.

3. Lens-induced uveitis cannot be suspected unless free lens material is in the eye or unless mature or hypermature cataract exists, permitting the possibility of spontaneous escape of lens material into the ocular cavities. A lens may appear mature anteriorly and be liquefied posteriorly, with leakage of lens substance into the vitreous cavity.

4. Finally, when one is in doubt, removal of the lens or lens remnants followed by an immediate favorable response would establish the diagnosis of lens-induced uveitis.

This quandary regarding the differential diagnosis of sympathetic ophthalmia, lens-induced uveitis, and other forms of uveitis is one in which every ophthalmologist finds himself at some time. We are grateful to Dr. Haik and his associates for pointing out the ramifications and complexities of the problem.

Dr. Dan M. Gordon, New York: Dr. Haik and his colleagues are to be congratulated upon an excellent piece of work, especially upon pointing out that we do not always know just what is sympathetic ophthalmia.

The hour is late, and I have no intention of adding gray hairs to an already aged meeting. However, I should like to comment briefly on the experience of my colleagues and myself in treating sympathetic ophthalmia. We find that chronic sympathetic ophthalmia is usually easily controlled when it flares up. We have had

excellent results with topical use of cortisone. However, in recent sympathetic ophthalmia the story is different. In our own experience with corticotropin and cortisone in the dosage used at present, corticotropin has proved by far the superior weapon. It is our opinion that once you have the bear by the tail, once you have clinically suppressed all the signs of sympathetic ophthalmia, you may possibly change your grip by discontinuing treatment for a day or two, but don't let go the tail, for if you do you will have trouble.

That means that after the acute stage some form of maintenance therapy should be worked out whether it is the administration of corticotropin at infrequent periods or the oral use of cortisone, which has been effective in cases in which it was not successful during the acute stage. In at least one very severe case of sympathetic ophthalmia following an intracapsular cataract extraction, we obtained an excellent result with corticotropin and then we stopped treatment; promptly, within a matter of days or weeks, severe bilateral optic neuritis developed, and, despite months of treatment with every weapon at our command, we have never been able to restore the patient to anything like her original status.

DR. RICHEY L. WAUGH JR., New Orleans: In behalf of the co-authors, I should like to thank the discussers for their excellent contributions. Although we have not attempted to evaluate the German literature, we have been impressed by a case reported by Krassó (*Ztschr. Augenh.* **83:** 77, 1934). After extraction of a senile cataract, typical sympathetic ophthalmia appeared. When the untraumatized, "sympathizing" eye was examined after enucleation because of the development of absolute glaucoma, a predominantly anterior uveitis was noted, along with spontaneous perforation of the lens capsule and infiltration of polymorphonuclear leucocytes and macrophages into the lens substance. Such observations, along with those already cited, lead us to ask whether other cases of sympathetic ophthalmia may not really have shown a bilateral form of endophthalmitis phacoanaphylactica and whether some of those cases of apparent sympathetic ophthalmia may have shown severer disease in a supposed sympathizing eye because of the presence there of antigen released from a supposedly intact lens to add to an anaphylactic process.

These questions also appear interesting in relation to Mackenzie's early description of clinical sympathetic ophthalmia. Mackenzie recognized sympathetic ophthalmia as developing only after trauma, and in no instance as following cataract extraction.

DR. GEORGE M. HAIK, New Orleans: We believe that the chief contribution of this paper may in time prove to be the emphasis on the necessity of a clinical differentiation of sympathetic ophthalmia and a bilateral form of endophthalmitis phacoanaphylactica, so that radically different methods of treatment may be prescribed for conditions superficially similar. In sympathetic ophthalmia removal of the eye may or may not be indicated; in a bilateral form of endophthalmitis phacoanaphylactica removal of the lens is imperative.

FAMILIAL GLAUCOMA

Report of a Pedigree

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THE RECOGNITION of the role played by hereditary factors in the etiology of glaucoma is not only of theoretical interest, but also of practical clinical importance. A carefully elicited genetic history often helps in the management of an established case of glaucoma. It also supplies important corroborative data toward the diagnosis of early glaucoma in a patient who has borderline intraocular tension.

The genetic approach thus becomes a valuable aid in the detection of new cases of glaucoma. If treatment is started in an early stage of the disease, much can be done toward prevention of blindness from glaucoma. This is one of the aims of the recently organized Heredity Clinic of the Manhattan Eye, Ear and Throat Hospital. With the aid of the New York State Commission for the Blind and other social agencies, it is hoped that other institutions may be stimulated to establish similar clinics, so that this case-finding program may be expanded.

The incidence of hereditary glaucoma has been variously estimated. In the series reported by Posner and Schlossman,[1] the proportion of patients giving a familial history was over 13% of the total number with glaucoma.

In most of the published pedigrees glaucoma appears to show dominant inheritance. In this form of heredity the disease may become manifest if only one of a pair of genes carries the defect. According to the Mendelian law, if one of the parents has glaucoma, 50% of the children will inherit the defective gene. In the case of adult glaucoma, the ratio of affected to normal sibs among the offspring of glaucomatous parents is not that high. The relatively lower actual incidence of glaucoma than the expected incidence is ascribed to lack of "penetrance" of the gene. Since it is not known what actually is the inherited factor in glaucoma, it must be assumed, as a tentative hypothesis, that there is a continuous gradation in the expressivity of the gene, so that some persons may be genetically glaucomatous but clinically normal. These persons may, nevertheless, transmit the disease to their progeny. This hypothesis may also help to explain the wide range in the severity of glaucoma observed clinically. Some patients have the disease in so mild a form that it may pass unrecognized unless a history of glaucoma in the family leads the ophthalmologist to conduct provocative tests and careful field studies. These mild

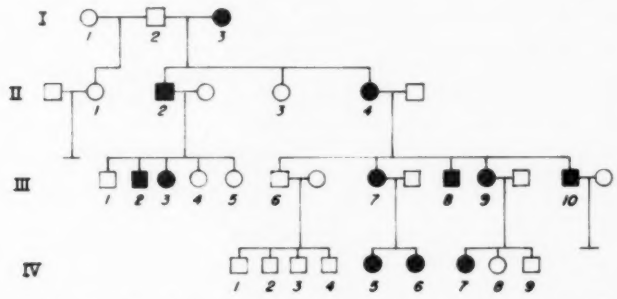
From the Heredity Clinic, Manhatten Eye, Ear and Throat Hospital.

1. Posner, A., and Schlossman, A.: Role of Inheritance in Glaucoma, Arch. Ophth. **41**: 125-150 (Feb.) 1949.

forms are not necessarily early glaucoma, since the patients may live for many years without showing any aggravation of the signs or symptoms, at least while under miotic therapy.

There is no essential difference in clinical manifestation between hereditary and nonhereditary glaucoma. Neither is there any difference in symptomatology between adult and juvenile glaucoma if one excludes the cases occurring in early childhood, in which the disease is probably dependent on a congenital malformation in the region of the angle of the anterior chamber. In fact, the line between adult and juvenile glaucoma is a purely arbitrary one and is fixed by most authors at the age of 35.

It is noteworthy, however, that in those families in which glaucoma occurs at an earlier age ("juvenile glaucoma") the pedigrees are more heavily loaded with affected members and, furthermore, the disease can usually be traced back for a greater number of generations. This fact may be explained by a greater penetrance of the gene. Whatever may be the nature of the inherited defect, it is probably more pronounced in these families. Hence, the disease tends to manifest itself at an



Pedigree of family with glaucoma simplex in four generations, showing dominant inheritance. Squares indicate males; circles, females; solid black figures, affected members. The six affected members of this kindred who have been observed and treated by us are III, 9 (propositus); III,7; III,10; IV,5; IV,6, and IV,7.

earlier age, and there are less apt to be persons with very mild or subclinical glaucoma.

A family in which the incidence of glaucoma was extraordinarily high and in which several members were affected at a relatively early age has come under our observation and is represented in the accompanying pedigree.

THE PEDIGREE

The first member of this kindred to have come to the attention of one of us (W. G. F.) is Barbara R. (III,9), who therefore is the propositus. She is one of five siblings, of whom all but one have glaucoma. The normal sib, Edward D. (III,6), has four sons, who thus far are all normal. On the other hand, only two of five children of the affected sibs are normal, and they are 17 and 6 years old, respectively.

One of the affected sibs, George D. (III,8), has bilateral asymptomatic chronic simple glaucoma, which was discovered by another ophthalmologist 31 years ago,

when the patient was 23. Operation was performed on both eyes, and he has retained normal visual acuity up to the time of this report. The three other sibs were treated by us, and their cases will be discussed in greater detail later.

The mother of this sibship, Barbara D. (II,4), had asymptomatic chronic simple glaucoma. The age of onset is not known, but the glaucoma probably began fairly early in life, since she was practically blind when the disease was discovered, at the age of 63. The father lived to the age of 85 and had normal eyes. The mother had a sister who died at the age of 33, leaving no children, and a brother who became blind from glaucoma and who left five children, of whom two have glaucoma. No detailed information could be obtained pertaining to this branch of the family.

It appears that the trait was transmitted to the propositus by her mother's mother, who also had glaucoma. The husband of the latter was normal, as was the husband's first wife. With his first wife he had a daughter who lived with her half-sister for many years, without showing any evidence of glaucoma.

The mode of inheritance of glaucoma in this pedigree appears to follow the lines of simple dominance, with a high degree of penetrance. Even though the disease tends to be discovered at an earlier age in the younger generations, this trend need not be interpreted as "anticipation," for when the glaucoma was discovered at a later age, it was usually present in a more advanced phase of its evolution. In all cases the glaucoma was of the chronic simple type. These cases, being thus clinically similar, may be regarded, in the absence of evidence to the contrary, as genotypically similar.

The case histories of the patients who were treated by us are briefly given.

REPORT OF CASES

Case 1.—B. R. (III,9), a woman aged 50, was first seen in 1925, when she was 24. At this time she complained of seeing colored rings about lights. This symptom worried her because her brother, two years older, had been operated on for glaucoma by another ophthalmologist two years previously.

Her eyes had never been red or painful; yet the tension measured 50 mm. in the right eye and 60 mm. in the left eye (Schiøtz). The disks showed slight pallor and nasal displacement of vessels. Vision was 20/15 in each eye with a correction of —1.50 D. for the right eye and of —1.25 D. for the left eye. The refractive error had not changed for many years.

Under treatment with pilocarpine nitrate 1%, the tension dropped promptly and fluctuated between 30 and 40 mm. for the next four years, the left eye tending to have the higher tension. The cupping and pallor of both disks increased. Progressive loss of the nasal field developed in the left eye, encroaching on the area of fixation, with a resulting drop in visual acuity to 20/100.

In 1929, a trephination with complete iridectomy was performed on the left eye, followed one week later by a trephination with peripheral iridectomy on the right eye.

The tension then dropped to levels of 16 to 20 mm. in each eye, where it has remained without the use of miotics.

The loss of field and increase in cupping of the optic nerve continued nevertheless. At the time of this report, the right eye shows an upper arcuate scotoma and has a corrected vision of 20/15. The left eye has lost all but the temporal periphery of the field and has a corrected vision of 20/200.

Case 2.—C. C. (III,7), a woman aged 56, was first seen on April 21, 1950, with the complaint that for three months she had been having difficulty in reading fine print. Visual acuity was 20/70 in the right eye and 20/100 in the left eye. Tension was 43 mm. in the right eye and 28 mm. in the left eye. There was loss of the lower half of the left field and of all but the lower temporal quadrant of the right field.

Under treatment with furtrethonium (furmethide®) iodide, 10%, the tension dropped at first to about 20 mm. in each eye, but in October it began to rise to between 35 and 45 mm. in the right eye and to between 26 and 29 mm. in the left eye. Visual acuity did not improve beyond 20/60 in either eye, and both eyes were practically emmetropic.

In December, 1950, trephination with peripheral iridectomy was performed on each eye.

The tension, when last measured, on Oct. 26, 1951, was 16 mm. in the right eye and 15 mm. in the left eye, and the visual acuity and visual fields have remained unchanged.

CASE 3.—J. D. (III,10), a man aged 47, was first seen in May, 1941, when he complained of recurrent irritation of the left eye for the past five years. Vision was 20/20 in the right eye and 20/30+ in the left eye. Tension was 32 mm. in the right eye and 45 mm. in the left eye. There was no cupping of the nerve head. Under treatment with pilocarpine nitrate, 1%, the tension dropped promptly to between 26 and 30 mm. in each eye. After several months it would again range from 30 to 40 mm., and the patient complained of occasional halos and poor twilight vision. While vision was 20/20 in each eye, the blind spot in the left eye showed moderate enlargement. In January, 1943, trephination with peripheral iridectomy was performed on each eye.

After the operations the symptoms were relieved, and no further change in the fields was noted. In April, 1950, the fundi were still normal; the tension measured 15 mm. in the right eye and 14 mm. in the left eye; vision was 20/20 in the right eye and had deteriorated to 20/30 in the left eye.

CASE 4.—V. C. (IV, 5), a woman aged 30, came for a routine examination in June, 1950, because of the family history of glaucoma. She had no symptoms. Vision was 20/20 in each eye without correction. Tension was 24 mm. in each eye. In February, 1951, the tension was 27 mm., and the water test of Marx and Schmidt resulted in a rise of 10 mm., to 37 mm., with a return to 27 mm. after two hours. The tension remained at 27 to 30 mm. in the succeeding months in spite of the use of pilocarpine, and even physostigmine.

CASE 5.—E. C. (IV, 6), a woman aged 26, had glaucomatous excavation and atrophy of both optic disks when she was first seen, in August, 1950, although she had never experienced any symptoms. Vision was 20/30 in each eye. Both fields showed generalized contraction, and there was loss of the upper nasal quadrant of the right field. Tension was 30 mm. in the right eye and 25 mm. in the left eye, and it fluctuated between 25 and 35 mm., in spite of the use of miotics, carbachol (doryl®) and physostigmine. Since the fields continued to deteriorate, bilateral trephination with peripheral iridectomy was performed in December, 1950.

In July, 1951, vision was 20/30, and the tension measured 16 mm., in each eye.

CASE 6.—P. R. (IV, 7) was first seen in 1942, at the age of 12 years, complaining of poor distant vision. Vision was corrected to 20/20 in each eye with a prescription of —1.00 sph.⌒—0.75 cyl., axis 180 for each eye. The tension was 22 mm. in each eye.

In 1943 the tension was 26 mm. in the right eye and 28 mm. in the left eye, and in 1944 it measured 35 mm. in the right eye and 26 mm. in the left eye. At this time the fields and fundi were normal. During the succeeding years the tension fluctuated between 21 and 27 mm., while the myopia increased to 3 D. In June, 1950, the tension was 30 mm. in each eye, and pilocarpine nitrate, 1%, was prescribed. In spite of miotic therapy, the tension remained 40 mm. in each eye. In June, 1951, trephination with peripheral iridectomy was done on each eye. In August, 1951, corrected vision was 15/15 in each eye, and the tension was 17 mm. in the right eye and 20 mm. in the left eye.

CASE 7.—J. R. (IV, 8) first complained of poor vision in 1945, at the age of 11 years. Vision could be corrected to 20/20 with —1.00 sph.⌒—0.50 axis 180 for the right eye and —0.75 sph.⌒—0.50 cyl., axis 180 for the left eye. Tension measured 17 mm. in each eye. The myopia has increased about ¾ D. to the time of writing, and the tension has remained between 17 and 18 mm.

COMMENT

This pedigree shows an unusually striking prevalence of glaucoma in a family in which there is no consanguinity and in which the mode of inheritance appears to be dominant.

The glaucoma tends to begin at an early age, and its progress appears to be favorably influenced by early operation. The response to trephination is uniformly good.

The glaucoma, at whatever age it occurs, shows no special features to distinguish it from other, apparently sporadic forms of adult chronic simple glaucoma.

The refractive errors are insignificant, the refractive condition varying from emmetropia to low myopia.

In most cases (four) the glaucoma was asymptomatic and was discovered only on routine examination. Two patients (III,9 and III,10) noticed recurrent colored halos. In one of these (III,10), as well as in an otherwise asymptomatic patient (IV,6), poor dark adaptation was noted, although this did not constitute a complaint.

CONCLUSIONS

The pedigree discussed illustrates the well-established fact that glaucoma may be not only familial, but definitely hereditary in certain families. It is usually inherited as a simple dominant. The inherited factor in glaucoma is as yet not known. A more widespread interest in the subject should lead to the collection of large numbers of pedigrees. Such an extensive study may throw light on this phase of the problem, thus contributing to knowledge of glaucoma in general.

To the practical ophthalmologist, an awareness of hereditary glaucoma often means earlier diagnosis and more effective treatment, resulting in a better prognosis for the patient.

The sociologic significance of a knowledge of the genetic factors in glaucoma lies in its offering a practical approach to the discovery of early cases, thus contributing materially to the prevention of blindness from glaucoma.

EFFECT OF CORTISONE UPON CORNEAL VASCULARIZATION PRODUCED EXPERIMENTALLY

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THE PURPOSE of this investigation is to determine the effect of cortisone on the formation of corneal vessels, the technique of formation and measurement of corneal vessels described by Campbell and Michaelson [1] being used. In this method a standard lesion of the cornea is produced by the application for a constant time of a platinum-wire cautery supplied with a constant voltage. The area of vascularization produced by the standard lesion is demarcated by India ink injected after the death of the animal.

METHOD

The experiments were carried out with rabbits of various weights. Prior to cauterization, 2 drops of 1% tetracaine hydrochloride was instilled into the conjunctival sac. The lesion was placed in the 12-o'clock meridian with its center about 2.5 mm. from the limbus. Precision in this matter, however, was not possible because of the difficulty in determining clinically the exact position of the limbus. The lesion was about 1 mm. in diameter and involved the epithelium and anterior two-thirds of the substantia propria. The ulcers were recauterized each day, the same cautery heated by the same voltage being used. Material for culture was taken from each ulcer during the period of the test. All the cultures were found to be sterile. In each animal both corneae were cauterized. Most right eyes received 1.25 mg. of cortisone acetate injected subconjunctivally close to the limbus in the 12-o'clock meridian. In some cases a single initial dose was given; in others three doses were given, spread throughout the 10-day period, while in others a daily injection was made. In most cases the left eyes were used as controls, some eyes receiving an injection of isotonic sodium chloride solution, while the others received an injection of cholesterol subconjunctivally in the 12-o'clock meridian whenever the fellow eye was treated with cortisone.

At the end of the serial cauterization the animals received a terminal injection of "prodor mol" (a barbituric-acid compound), and 10 to 15 ml. of India ink was injected under a pressure of 100 to 150 mm. Hg into each carotid artery. The eyes were excised and placed in 10% formalin for 24 hours. The appropriate portion of the cornea was then excised and mounted in glycerin (Figure). The vascular area was measured with a microscope eyepiece micrometer. The following measurements were made in each case: (1) the size of the ulcer, (2) the distance between the ulcer and the limbus, (3) the height of the vascular triangular area, and (4) the base of the vascular area. Even with the aid of the microscope it is not always easy to determine the normal limbal limit of the vessels. This may vary from animal to animal. Aids in detection are the normal limbal limit as observed on either side of the vascular area; the size of the vessels, the new-formed vessels being usually only of capillary size within the period of the investigation, and the edge of the limbal pigmentation. The last-mentioned structure is not always a secure guide, as there is often a pigmentary, as well as a vascular, proliferation in the region of the ulcer.

1. Campbell, F. W., and Michaelson, I. C.: Brit. J. Ophth. **33**:248, 1949.

As the triangle of vascularization appears to be practically always isosceles, the extent of the area of vascularization was estimated from the height and the length of the base. In some eyes there was irregularity of the triangular formation because of the tendency of the vessels to grow around either side of the ulcer after reaching it. In these cases the area was likewise estimated from the height and the base length, no correction being made for the irregularity of the apex of the triangle.

RESULTS

The results are given in the accompanying table. It will be noted that in several eyes measurements are not given because of the unsatisfactory injection.

Size of the Ulcer.—For 30 untreated eyes the mean size of the ulcer was 1.3 ± 0.26 mm.; for 21 treated eyes the mean size of the ulcer was 1.3 ± 0.20 mm.

So far as the size of the ulcer is concerned, it would appear that the lesions in the two groups are similar. Only the ulcer of the right eye of Rabbit 10 and the ulcer of the left eye of Rabbit 12 are considerably beyond the mean size.

The excised cornea is mounted in glycerin. The ulcer and the triangular area of vascularization can be seen. The vessels are filled with India ink.

Distance of Ulcer from Limbus.—For 30 untreated eyes the mean distance was 2.4 ± 0.41 mm.; for 21 treated eyes the mean distance was 2.3 ± 0.55 mm.

It is clear that the mean and the scatter around the mean in the two groups are sufficiently similar for the purpose of comparing vascularization in treated and untreated eyes, as will be done in this investigation.

Areas of Vascularization.—For 30 untreated eyes the mean extent of vascularization was 5.7 ± 2.14 sq. mm.; for 21 treated eyes the mean extent was 3.2 ± 2.3 sq. mm.

The observed difference of the means is 2.5 sq. mm. The standard deviation of the difference of the means is 0.65 sq. mm. As the observed difference of the means exceeds three times the standard deviation, one may conclude that the results are highly significant.

As the area of vascularization clearly is affected by the distance of the ulcer from the limbus, comparison of the areas of vascularization in treated and untreated eyes must take into consideration the distance of the ulcer from the limbus.

Extent of Vascularization When Ulcer Is 2.0 Mm. or Less Distant from the Limbus: For 11 untreated eyes the mean extent was 7.4 ± 2.4 sq. mm.; for 13 treated eyes the mean extent was 4.2 ± 2.46 sq. mm.

Effect on Experimental Corneal Vascularization of Cortisone Treatment in Rabbit Eyes

	Untreated Eyes						Treated Eyes						
Rabbit No.	Eye	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Extent of Vascular Area, Sq. Mm.	Eye	Ulcer-Limbus Distance, Mm.	Height of Vascular Area, Mm.	Base of Vascular Area, Mm.	Size of Ulcer, Mm.	Extent of Vascular Area, Sq. Mm.	No. of Doses of Cortisone
1	R. E.	2.3	1.3	6.0	1.0	3.9							
	L. E.	2.0	1.5	7.5	1.1	7.5							
2	R. E.	2.3	2.3	6.5	1.0	7.5							
	L. E.	3.0	1.6	6.8	1.6	5.4							
3	R. E.	2.6	1.4	7.0	1.8	4.9							
	L. E.	2.0	1.9	7.0	1.5	6.7							
4	R. E.	2.9	1.6	5.5	1.3	4.3							
	L. E.	2.3	1.4	6.5	1.0	4.6							
5	L. E.		Unsatisfactory injection				R. E.	3.2	0.8	7.0	1.1	2.8	1
6	L. E.	2.4	1.5	6.0	1.5	4.5	R. E.	3.7	0.5	5.5	1.5	0.8	1
7	L. E.	2.5	0.9	7.5	1.8	3.4	R. E.	2.5	0.9	6.0	1.9	2.7	8
8	L. E.	2.4	1.0	6.3	1.5	3.2	R. E.		Unsatisfactory injection				
9	L. E.	2.6	1.5	6.0	1.0	4.5	R. E.		Unsatisfactory injection				
10	L. E.	3.6	1.0	5.0	1.5	2.5	R. E.	3.3	0.8	5.0	1.1	1.9	3
11	L. E.	3.0	2.0	6.3	1.3	5.1	R. E.	3.0	0.3	4.0	1.0	0.6	3
12	L. E.	2.5	0.8	6.8	0.7	2.7	R. E.	2.0	1.0	4.0	1.1	2.0	10
13	L. E.	2.5	1.8	5.0	1.5	4.5	R. E.	1.9	1.3	5.3	1.5	3.4	10
14	L. E.		Unsatisfactory injection				R. E.	2.3	0.6	3.3	1.3	1.0	10
15	L. E.	2.7	1.3	5.5	1.8	3.6	R. E.	2.0	1.3	4.0	1.3	2.6	3
16	L. E.	2.8	1.3	5.8	1.3	3.8	R. E.	2.8	0.3	3.3	1.0	0.5	3
17	L. E.	1.8	1.3	8.0	1.3	5.2	R. E.	1.8	1.3	4.8	1.3	3.9	3
18	L. E.	2.0	1.5	7.5	1.3	5.7	R. E.	2.5	1.5	3.5	1.5	2.8	3
19	L. E.	2.0	1.3	6.5	1.3	4.6	R. E.	1.8	1.0	4.8	1.3	2.4	3
20	L. E.	2.5	1.6	6.8	1.3	5.4	R. E.	1.8	1.8	4.0	1.3	3.6	10
21	L. E.	2.1	2.1	7.0	1.3	7.4	R. E.	2.0	1.3	4.5	1.3	3.0	10
22	L. E.	2.1	2.1	7.6	1.3	8.0	R. E.	2.0	1.3	5.8	1.3	3.8	3
23	L. E.	2.0	2.5	7.5	1.3	9.4	R. E.	1.7	1.7	5.0	1.3	4.3	3
24	L. E.		Unsatisfactory injection				R. E.	2.0	1.1	5.0	1.3	2.8	3
25	L. E.	2.0	2.3	7.5	1.5	8.6	R. E.		Unsatisfactory injection				
26	L. E.	1.8	1.8	7.5	1.5	6.8	R. E.	2.0	1.4	8.0	1.3	5.6	1
27	L. E.	2.0	2.4	10.0	1.3	12.0	R. E.	2.0	2.4	10.0	1.3	12.0	1
28	L. E.	2.0	2.7	8.0	1.4	8.4	R. E.		Unsatisfactory injection				
29	L. E.	2.0	1.6	7.5	1.0	6.0	R. E.	1.9	1.3	7.5	1.5	4.9	1

The observed difference of the means is 3.2 sq. mm. The standard deviation of the difference of the means is 0.65 sq. mm. and is therefore one-fifth the observed difference of the means. The results are therefore highly significant.

Extent of Vascularization When Ulcer Is 2.1 to 2.9 Mm. Distant from Limbus: For 16 untreated eyes the mean extent was 4.8 ± 1.53 sq. mm.; for 4 treated eyes the extents were 0.5, 1.0, 2.7, and 2.8 sq. mm.

Extent of Vascularization When Ulcer Is 3.0 to 3.7 Mm. Distant from Limbus: For three untreated eyes the extents were 2.5, 5.1, and 5.4 sq. mm.; for four treated eyes the extents were 0.6, 0.8, 1.9, and 2.8 mm. These differences are fairly clear-cut and may probably be accepted as significant.

Comment on Effect of Cortisone on Area of Vascularization: It would appear that in the circumstances of these experimental conditions cortisone in the doses given is capable of reducing corneal vascularization by about 45%. The following tabulation emphasizes the effect of the distance of the ulcer on the reduction of the area of vascularization:

Distance of Ulcer from Limbus, Mm.	Mean Area in Untreated Eyes, Sq. Mm.	Mean Area in Treated Eyes, Sq. Mm.	Diminution of Area, %
2.0 or less	7.4	4.2	43
2.1-2.9	4.8	1.7	65
3.0 or more	4.3	1.5	65

It would appear that the farther the ulcer is from the limbus, the greater the effect of cortisone in diminishing the area of vascularization.

Height of Vascularized Area.—For 30 untreated eyes the mean height was 1.6 ± 0.48 mm.; for 21 untreated eyes the mean height was 1.1 ± 0.51 mm.

The observed difference of means is 0.5 sq. mm. The standard deviation of the difference of the means is 0.14 sq. mm. and is therefore less than one-third the observed difference of the means. The findings are therefore highly significant.

Comment on Effect of Cortisone on Height of Vascular Area: As the experiment lasted 240 hours, an approximate estimation can be made of the rate of vessel growth in the 12-o'clock meridian of the cornea, that is, the meridian in which the ulcer is placed. The estimate is made from the mean heights given above. For the untreated eyes the rate of vessel growth was

$$\frac{1.6 \times 1,000}{240} = 6.7\ \mu \text{ per hour}$$

For the treated eyes the rate of vessel growth was

$$\frac{1.1 \times 1,000}{240} = 4.6\ \mu \text{ per hour}$$

It would appear in the circumstances of the experiment that in the untreated eyes endothelial-cell division in the capillaries takes place at the rate of about one cell division per hour and that under the influence of cortisone in the dosage given this rate can be reduced by about 30%. The following tabulation indicates the effect of the distance of the ulcer on the reduced rate of vessel growth:

Distance of Ulcer from Limbus	Mean Rate in Untreated Eyes, μ/Hr.	Mean Rate in Treated Eyes, μ/Hr.	Slowing of Rate of Vessel Growth, %
2.0 or less	7.5	5.8	23
2.1-2.9	6.3	3.3	48
3.0 or more	6.3	2.5	60

It would appear that the farther the ulcer is from the limbus, the greater the effect of cortisone in slowing longitudinal growth of the capillaries.

Effect of Frequency of Administration of Cortisone on Area of Vascularization.—In order to exclude the factor of distance of the ulcer, only the eyes were considered in which the distance of the ulcer from the limbus was 2.0 mm. or less.

No. of Doses of 1.25 Mg. Cortisone	Mean Area of Vascularization, Sq. Mm.
1 (2 eyes)*	5.3
3 (6 eyes)	3.3
10 (4 eyes)	3.0

* Owing to the small size of this group, the extraordinary result in Rabbit 27 has been omitted.

It would appear, therefore, that for the distance of 2.0 mm. or less a single dose of cortisone has little effect. However, in Rabbit 6 the area of vascularization was only 0.8 sq. mm., despite administration of only one dose of cortisone. In this animal the distance of the ulcer was 3.7 mm. from the limbus, which approximates the limit beyond which vessel growth does not take place (Campbell and Michaelson [1]). The area of vascularization in this animal should be compared with the area (2.5 sq. mm.) in the untreated eye of Rabbit 3, in which the distance of the ulcer was very similar (3.6 mm.). It may be generally concluded that a single dose has little effect on the vascularization unless the ulcer is far from the limbus and that 3 doses during the 10-day period are as effective as 10 doses.

Influence of Other Factors on the Cortisone Effect.—In these experiments efforts have been made to neutralize the effects of differences in the severity of the lesion and its distance from the limbus. It is possible that other factors, such as the age of the animal and its nutritional state, may have influenced the effect of the cortisone. These factors can be excluded by a consideration of those animals in which the lesion was by fortune placed at almost equal distances from the limbus in the two corneae. This circumstance was obtained in Animals 7, 11, 16, 17, 21, 22, 27, and 29.

Animal No.	Limbus-Lesion Distances, Mm.	Area of Vascularization in Untreated Eyes, Sq. Mm.	Area of Vascularization in Treated Eyes, Sq. Mm.	No. of Doses of Cortisone
21	2.1 and 2.0	7.4	3.0	10
11	3.0 and 3.0	5.1	0.6	3
7	2.5 and 2.5	3.4	2.7	3
16	2.8 and 2.8	3.8	0.5	3
17	1.8 and 1.8	5.2	3.9	3
22	2.1 and 2.0	8.0	3.8	3
27	2.0 and 2.0	12.0	12.0	1
29	2.0 and 1.9	6.0	4.9	1

If the differences in areas of vascularization in the treated and the untreated eyes of this group are estimated and analyzed in connection with the factors of distance and frequency of cortisone administration as has already been done for the eyes as a whole, it can be seen that the findings are similar to those for the whole series of eyes. As age or nutritional state would presumably affect the two eyes of the same animal equally, it may be concluded that these factors played no significant role in determining the effect of cortisone in this series of animals as a whole.

CONCLUSIONS

The method of producing new vessels in the cornea and their measurement as described appears to be a suitable one for the purpose of the experiment. Since a difference of 1 mm. in the ulcer-limbus distance has a significant influence on the extent of the area of vascularization and on the rate of new-vessel growth, it is important to use a method which permits of as exact measurement as possible. Microscopic measurement has therefore an advantage over clinical measurement.

Consideration of the results in which the lesions in the right and the left cornea were exactly equidistant from the limbus ("paired eyes") and comparison of these results with those obtained for the whole series are of importance. By this consideration the influence of age, nutrition, and other individual factors (within the experimental group of animals) on the results can be excluded. These individual factors may conceivably affect the response of the vascular growth to cortisone. It can be observed that there is a fairly wide variation in vascularize-

tion within the untreated eyes of the series. This emphasizes the necessity (1) of checking the results for the whole series by considering the results for paired eyes, as has been done above, and (2) of using as controls eyes within the series of animals being treated. This has been done, with a few exceptions, in this study.

Cortisone, even in small and infrequent doses, can affect the relatively dense corneal vascularization produced by a traumatic aseptic lesion placed close to the limbus. This result confirms clinical experience and the experimental work of Jones and Meyer.[2]

The effect is dependent on the distance of the lesion from the limbus, that is, on the degree of vascularization and on the frequency with which the cortisone is given. There appears, however, to be no special advantage in giving the drug subconjunctivally more than once in three days.

It has been suggested (Campbell and Michaelson [1]) that new-vessel formation in the cornea in the circumstances described involves a factor released by the lesion and diffusing from the site of the lesion to the preexisting limbal vessels. No evidence has been adduced here regarding the immediate mode of action of the cortisone. It may act by depressing the response of the vascular endothelium to the factor mentioned or by neutralizing the factor before it reaches the vascular endothelium. The depression of the rate of mitosis in the budding capillaries as the result of cortisone, as found in this series, does not elucidate this point. Other factors, such as, vitamins, radiation, and aqueous fluid, may apparently influence new-vessel growth in the cornea. The method of investigation described may be useful not only in assessing the effect of cortisone, but in comparing that effect with other factors capable of influencing the vessel growth.

SUMMARY

A method of producing fairly standard areas of new-vessel growth in the cornea of the rabbit is described. The necessary precautions in assessing the results are noted.

It has been shown that in the circumstances of the experiment 1.25 mg. of cortisone acetate injected subconjunctivally reduced the extent of the standard vascular area by about 45% and the rate of longitudinal capillary growth by about 30%.

The farther the ulcer which provokes the new-vessel growth is from the limbus, the greater is the effect of cortisone in reducing the area of vascularization and the rate of longitudinal growth of the capillaries.

A subconjunctival dose of cortisone every three or four days appears to be as effective as daily doses.

The site of action of cortisone is discussed.

NOTE.—Since the completion of this report, Lister and Greaves [3] and Ashton, Cook and Langham [4] have published results that are similar to those reported in this study.

Miss Eva Lewkowitz gave technical assistance.

This work was supported by a grant from the National Council to Combat Blindness, New York.

2. Jones, J. R., and Meyer, K.: Proc. Soc. Exper. Biol. & Med. **74**:102, 1950.
3. Lister, A., and Greaves, D. P.: Brit. J. Ophthal. **35**:725, 1951.
4. Ashton, N.; Cook, C., and Langham, M.: Brit. J. Ophthal. **35**:718, 1951.

INTRAOCULAR RUBBER FOREIGN BODIES AFTER SURGERY

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AFTER intraocular surgery foreign material is noted occasionally in the ocular tissues clinically and very often histologically. In some cases the foreign material may act as a toxic substance, effecting a postoperative inflammatory reaction. Duszynski [1] recently reported on this problem with special reference to lint from drapes and powder used on gloves. He presented photomicrographs, taken with polarized light, of ocular tissues after glaucoma surgery. Foreign material was surrounded by granulomatous tissue.

In 1928 Doherty [2] reported a case in which presumed India-rubber foreign particles were first noted 11 years after an extracapsular cataract extraction. Six red particles, 1 to 2 mm. in diameter, were seen in the iris crypts, without inflammatory reaction or fibrosis. It was believed that the particles were rubber introduced by an irrigating system with a rubber bulb. In 1948 Doherty [3] mentioned three cases of rubber foreign bodies in the eye and stated that definite harm was done in one case.

PRESENT INVESTIGATION

It is the purpose of the present paper to report seven cases of intraocular surgery in which rubber was introduced from a rubber irrigating bulb.

CASE 1.—On Feb. 12, 1951, during irrigation of the anterior chamber after extracapsular cataract extraction, numerous tiny red particles were seen entering the chamber from the irrigating cannula.[4] The particles, varying in size from 0.1 to 0.4 mm., immediately became lodged in iris crypts, as well as adherent to the posterior surface of the cornea and the posterior capsule of the lens. On the first postoperative day, the red particles were readily seen, and the anterior chamber was clear. Forty-eight hours after operation a massive hyphema, with ocular tension of 67 mm. (Schiøtz), was present and was treated by release of blood through the wound. One month after operation more than 35 red foreign particles were seen in the eye, some adherent to the posterior corneal surface, some in the iris crypts, and others adherent to the posterior lens capsule (Fig. 1). Two months after operation, the eye was white; the anterior chamber showed no cells or flare, and vision with a correction of +12.00 sph. ⊃ —1.00 cyl., axis 10 was 20/20 —1. Eight months after operation the eye showed that the foreign particles were unchanged, and there was no evidence of inflammation or fibrosis.

In six additional cases, with operations by various surgeons 6 to 18 months previously, small red foreign particles clinically similar to those seen in the first

1. Duszynski, L. R.: Contamination of Operative Wounds with Cotton Fibrils and Talc, Tr. Am. Acad. Ophth. **55**:110-115 (Nov.-Dec.) 1950.

2. Doherty, W. B.: India Rubber in Anterior Chamber: Report of Case; Also Description of Anterior Chamber Irrigator, Am. J. Ophth. **11**:16-17 (Jan.) 1928.

3. Doherty, W. B.: Use of Glass Irrigator for Anterior Chamber, Arch. Ophth. **39**:818-819 (June) 1948.

4. Dr. W. Morton Grant called attention to these particles at the time of operation.

case have been observed. In all cases irrigation of the anterior chamber had been performed with similar equipment.

Case 2.—On Jan. 9, 1951, an attempted intracapsular extraction of a hypermature cataract was complicated by rupture of the capsule. Irrigation of the anterior chamber was performed, and it was believed that no capsular material was left in the eye. There was moderately severe postoperative iridocyclitis which cleared after three weeks of local use of cortisone and mydriatic therapy. Six weeks after operation two red foreign particles were seen (Fig. 2). The upper particle was adherent to the face of the vitreous, the lower particle being in the vitreous

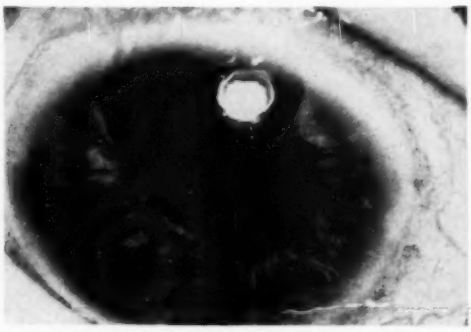

Fig. 1 (Case 1).—Photograph taken one month after operation, showing rubber foreign particles in the pupil and on the iris.

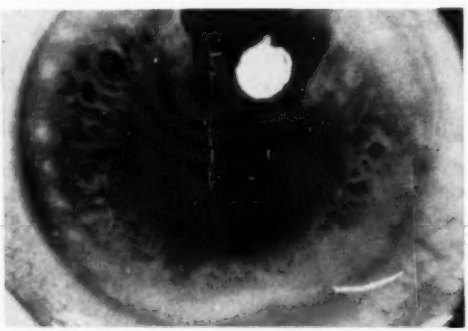

Fig. 2 (Case 2).—Photograph taken six weeks after operation, showing rubber foreign particles in the pupil.

itself. No fibrotic reaction was evident around the particles, nor has any developed during the nine-month period since operation. Corrected vision has remained 20/25.

Case 3.—On April 23, 1951, an attempted intracapsular extraction was complicated by rupture of the capsule as the lens was almost delivered. Irrigation was done, and all cortical and capsular material was removed. Three weeks after operation there developed a shallow anterior chamber, with separation of the choroid, which receded after removal of the corneoscleral sutures. At that time a red foreign particle was first seen adhering to the hyaloid membrane without fibrosis. The eye has remained free of inflammation for six months, with corrected vision of 20/50.

CASE 4.—An extracapsular cataract extraction in the right eye, on Jan. 21, 1950, was followed by severe plastic uveitis in both eyes, thought to represent either sympathetic ophthalmia or phacoanaphylaxis.

One year later an attempted intracapsular extraction in the left eye resulted in inadvertent rupture of the lens capsule. Considerable irrigation was done in an effort to remove lens material. There was moderate postoperative iridocyclitis in the left eye only, and this cleared after two months with local use of cortisone and mydriatic therapy. After the operation two red foreign particles were seen in the iris crypts and another in some lens material. No fibrosis developed about the foreign particles, and the eye has remained white for over eight months.

CASE 5.—In January, 1951, an extracapsular extraction for traumatic cataract was done, with irrigation of the anterior chamber. The eye showed signs of irritation for several weeks after operation, and a pupillary membrane developed. Red foreign particles were present in the iris crypts and in the pupillary membrane. However, fibrosis was not evident about the particles, the membrane being of the same density throughout.

CASE 6.—On Feb. 22, 1951, iridectomy for secondary glaucoma was performed on the sympathizing eye in a case of sympathetic ophthalmia. Irrigation was done because of bleeding.

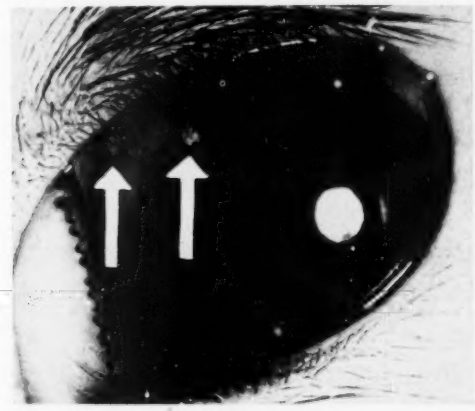

Fig. 3 (Experimental Rabbit).—Photograph taken three days after introduction of rubber particles.

Recurrent bouts of iridocyclitis have occurred since operation. A red foreign body has been lodged in an iris crypt, with no fibrotic membrane around it, although the eye has been inflamed for over seven months.

CASE 7.—On April 18, 1950, an intracapsular cataract extraction was performed, with irrigation of the anterior chamber. Postoperative healing was uneventful, and corrected vision was 20/30. One year later a red foreign particle was seen in the healed corneal wound, the appearance of the wound being similar throughout.

Experimental Study.—Particles of rubber were scraped from the inside of the irrigating bulb used in Case 1 and introduced through keratome incisions into two rabbit eyes. In Figure 3 the rubber foreign particles are shown three days after introduction. At the 10-o'clock meridian, in the keratome wound, is a clump of three pieces of rubber, and another clump, of four pieces of rubber, is seen lying on the anterior surface of the iris at 11 o'clock. The rabbit eyes were kept under observation for three months, there being no signs of inflammation, and biomicroscopic study revealed no fibrosis about the particles.

COMMENT

In the operative cases described, a rubber bulb fitted with an anterior-chamber-irrigating tip had been used. The rubber bulb used in Case 1 was cut open. The bulb had been manufactured from two hemispheres cemented on the inside, and along the seam many loosely adherent particles of rubber were evident (Fig. 4). These particles, which resembled those in the eyes described, could be easily dislodged from the surface of the bulb by a stream of water. Doherty [5] has described a glass

Fig. 4.—Inside seam of rubber irrigating bulb used in Case 1. Note the loosely adherent particles.

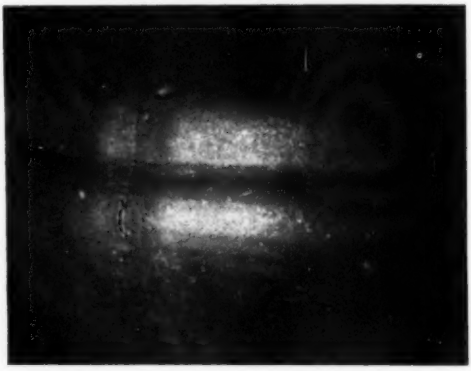

Fig. 5.—Inside seam of a rubber bulb which is not cemented on the inside.

cannula with a dilated chamber for observation of foreign particles coming from the rubber bulb. Use of this apparatus has two disadvantages: 1. The glass tip of the irrigator may be broken, with introduction of glass into the eye. 2. The surgeon is obliged to divide his attention between the area being irrigated and the glass chamber in the cannula. Heath [6] has devised a stubby glass syringe to which is attached

5. Doherty.[2,3]

6. Heath, P.: Anterior Chamber Irrigator, Tr. Sec. Ophth. A. M. A., p. 260, 1937.

a metal irrigating cannula. This offers complete protection against introduction of foreign bodies, but some surgeons believe that the rubber bulb gives better control of the irrigating stream. Rubber bulbs which are not cemented on the inside are available (Fig. 5). No loose foreign particles are present, the inner surface being smooth. Such a bulb, thoroughly rinsed out before irrigation, is obviously better than that pictured in Figure 4. A fine filter which could be easily cleaned and sterilized might be developed to be inserted in the cannula.

In all the seven cases presented there were observed typical red foreign particles, which to date showed no fine membrane or fibrosis about them. In his series of three cases, Doherty [5] stated that no irritation was present in any of the eyes but that a fine secondary membrane held the foreign particles in position. The absence, clinically, of such a membrane in the present series may be a consequence of the relatively short time the foreign particles have been in the eyes. In Case 2 moderately severe postoperative iridocyclitis occurred, which may, in part, have been aggravated by the presence of rubber in the vitreous. However, when the inflammatory process subsided, the foreign bodies were not involved in a fibrotic membrane, and even during the active inflammation the vitreous itself was not affected. In Case 3 a rubber particle was adherent to the hyaloid membrane without signs of irritation. In Cases 4, 5, and 6 postoperative inflammation was present. In each case, however, the inflammation probably resulted from other causes, as described, although the rubber particles may have added to the picture. It would appear that the anterior segment and the vitreous tolerate rubber foreign particles well.

SUMMARY

A case is presented in which rubber foreign particles were seen entering the anterior chamber; six cases with similar clinical foreign particles in the eye are described.

A toxic, irritating effect of rubber foreign bodies was not evident in this series of seven human eyes and in two experimental rabbit eyes.

The prevention of inadvertent introduction of rubber foreign bodies by irrigation is discussed.

Dr. David D. Donaldson supplied the photographs in Figures 1 and 2.

SUBHYALOID HEMORRHAGE AND EXOPHTHALMOS DUE TO RUPTURED INTRAVENTRICULAR ANEURYSM

A Case Occurring in Toxemia of Pregnancy

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A SUBHYALOID hemorrhage is an intraocular collection of blood that remains contained in a self-created, previously nonexistent space, usually between the posterior limiting layer of the vitreous and the retina. Thus it is entirely separate and distinct from the intraretinal hemorrhage, associated, e. g., with hypertension and diabetes, and from the vitreous hemorrhage, of traumatic or diabetic origin.

Subhyaloid (or preretinal) hemorrhage is rare. The first case was reported by Liebreich [1] in 1863, and others have been recorded, although infrequently.[2]

The intraocular pathology was at first believed to stem from the arteries,[3] but later papers [4] indicate the venous origin of the subhyaloid hemorrhage, an explanation which is undoubtedly the true one.

Clinically, subhyaloid hemorrhages are seen as dark-red masses, which most frequently are circular, occur at the posterior pole, and are usually extensive. They may be single, in which case the hemorrhage is large, up to 10 or 12 mm. in diameter, or multiple, in which case they are generally round, usually measuring 1 or 2 disk diameters, and scattered about the fundus like pebbles. It has been noted that there is often a settling of the blood in these hemorrhages, so that the erect position produces a curved inferior line with a horizontal, or "fluid," level superiorly.[5]

The exact size of this intraocular hemorrhage was thought to be between the intact retina and the vitreous; later this concept was changed to localization of the hemorrhage between the nerve fiber layer and the internal limiting membrane of the retina. It has been shown that the posterior limiting layer of the vitreous

1. Liebreich, R.: Atlas der Ophthalmoscopie, Berlin, A. Hirschwald, 1863, Table 8, Pt. 2; cited by Duke-Elder, S.: Text-Book of Ophthalmology, Vol. III, St. Louis, C. V. Mosby Company, 1941.

2. (*a*) Duke-Elder, S.: Text-Book of Ophthalmology, Vol. III, St. Louis, C. V. Mosby Company, 1941. (*b*) MacDonald, A. E.: Ocular Lesions Caused by Intracranial Hemorrhage, Tr. Am. Ophth. Soc. **29**: 418-432, 1931.

3. Nettleship, E., in discussion on Morton, A. S.: Haemorrhage in Region of Macula, Tr. Ophth. Soc. U. Kingdom **4**:149, 1884.

4. Fisher, J. H.: A Case of Subhyaloid Haemorrhage, in Which the Specimen Was Obtained with Microscopic Sections, Roy. Lond. Ophth. Hosp. Rep. **14**:291-305, 1886.

5. Masselon, J.: Observations on Movement of Blood in Subhyaloid Hemorrhages, Clin. Ophth. **1**:19, 1895. Duke-Elder.[2a]

is identical with the internal limiting membrane of the retina.[6] The commonest mechanism, undoubtedly, is that shown in the first case in which pathologic examination was made.[4] The rapid increase in venous pressure causes rupture of the venules just beneath the internal limiting membrane. The blood poured out beneath the internal limiting membrane easily strips off and raises the membrane, thus forming a distended sac. In cases in which this artificially created container ruptures, there is dissemination of the hemorrhage throughout the vitreous. In such cases the details of the fundus are completely obscured, and it is impossible to differentiate ophthalmoscopically a hemorrhage of this type from the vitreous hemorrhage produced by other mechanisms.[7]

The extraocular pathogenetic factor in the majority of cases is sudden, rapid increased intracranial pressure. Although trauma, coughing, toxic states, hematopoietic diseases, menstrual disorders, pneumoencephalography, and papilledema have been recorded as the causes of subhyaloid hemorrhages, the commonest cause of the increased intracranial pressure is subarachnoid hemorrhage.[8] The causes of subarachnoid hemorrhage are spontaneous rupture of intracranial aneurysms, vascular accidents, trauma, and bleeding from vascular and necrosing tumors. The rupture of an intraventricular berry aneurysm with production of a subarachnoid hemorrhage is a rare cause of subhyaloid hemorrhage.[8b]

The literature contains references to cases of retinal hemorrhages in the course of pregnancy,[9] but these are of the intraretinal type. A review of the literature has failed to show a case similar to the one to be reported, in which rupture of an intraventricular berry aneurysm in the course of toxemia of pregnancy gave rise to a subhyaloid hemorrhage and to exophthalmos.

REPORT OF A CASE

M. K. M., a Negro woman aged 34 in the 35th week of pregnancy, was brought to the hospital in a comatose condition. The pregnancy was her sixth, the first four having been essentially normal and the fifth having been accompanied by signs of toxemia (albuminuria and hypertension).

The patient had been essentially well until two hours prior to her admission to the hospital, when she complained of a severe frontal headache and the feeling of "becoming paralyzed." She then became comatose, and the right eye began to bulge. An ambulance was called, and the blood pressure recorded by the intern on the ambulance was 200/140.

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6. Mann, I.: Nature and Boundaries of the Vitreous Humor, Tr. Ophth. Soc. U. Kingdom **47**:172, 1927.

7. (*a*) Fisher, J. H.: Drawing of Semilunar Retinal Haemorrhage (So-Called Subhyaloid Haemorrhage), Proc. Roy. Soc. Med. **6**:21-23, 1912. (*b*) Riddoch, G., and Goulden, C.: On the Relationship Between Subarachnoid and Intraocular Haemorrhages, Brit. J. Ophth. **9**:209-223, 1925.

8. (*a*) Riddoch and Goulden.[7b] (*b*) Walsh, F. B.: Clinical Neuro-Ophthalmology, Baltimore, Williams & Wilkins Company, 1947. (*c*) Symonds, C. P.: Spontaneous Subarachnoid Haemorrhage, Quart. J. Med. **18**:93-122, 1924. (*d*) A case of subhyaloid hemorrhage following pneumoencephalography presented by F. B. Walsh, at Saturday Conference, July 7, 1951, Johns Hopkins Hospital.

9. (*a*) Duke-Elder.[2a] (*b*) Ballantyne, A. J.: The Ocular Manifestations of Spontaneous Subarachnoid Haemorrhage, Brit. J. Ophth. **27**:383-414, 1943. (*c*) Hallum, A. V.: Retinal Arterioles in the Hypertensions of Pregnancy, Tr. Am. Ophth. Soc. **43**:585-607, 1945. (*d*) Nemecskay, T.: Retinal Hemorrhage During Pregnancy, Zentralbl. Gynäk. **65**:1572-1575, 1948.

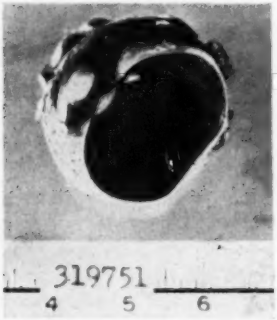

Fig. 1.—Gross photograph of the left eye, showing subhyaloid hemorrhage, measuring 7 by 11 mm., in the area of the macula and disk. Note how the vitreous is completely transparent. The hemorrhage has been contained in one area. Armed Forces Institute of Pathology Accession No. 319571.

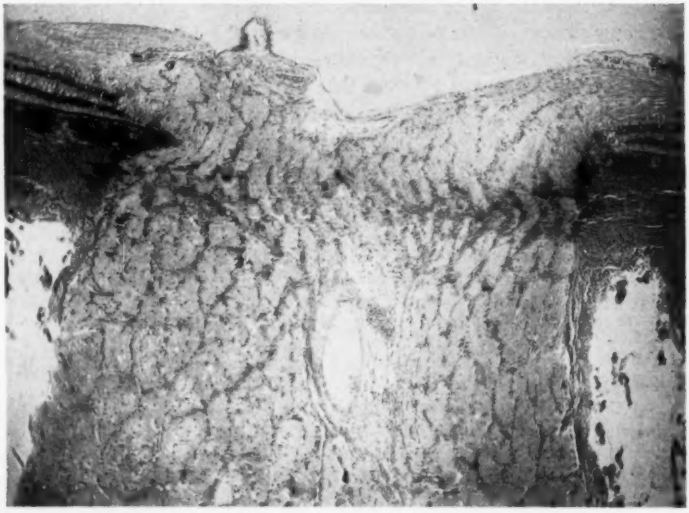

Fig. 2.—Section through the optic nerve of the left eye (× 48). Note that the lamina cribrosa is pushed somewhat anteriorly, indicating early or moderate papilledema. On the right may be seen a few red blood cells, raising the internal limiting membrane of the layer. This was the nasal extent of the subhyaloid hemorrhage. Armed Forces Institute of Pathology Accession No. 319751.

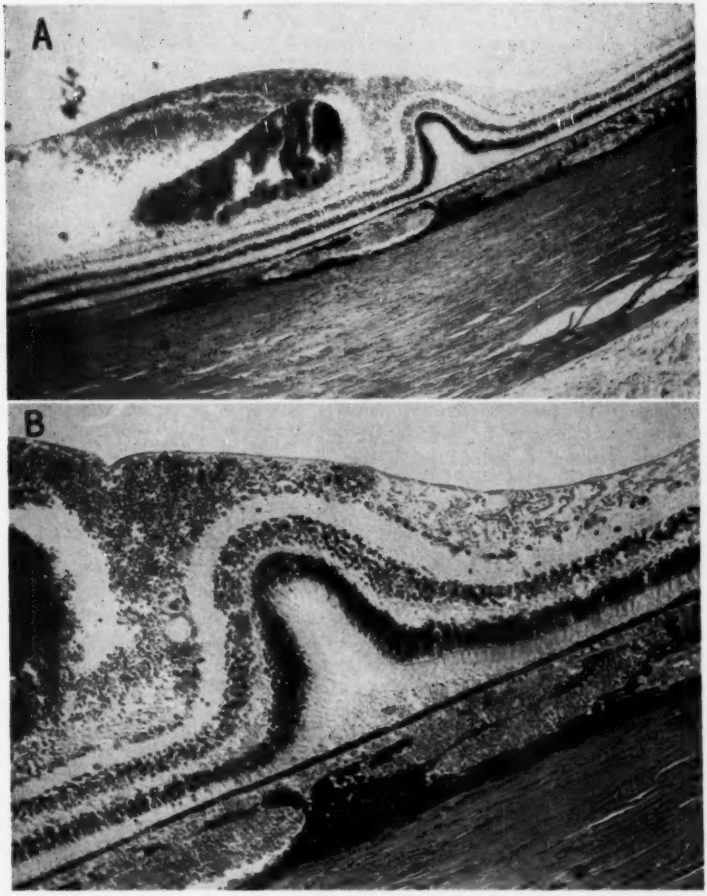

Fig. 3.—*A*, section through subhyaloid hemorrhage, in the left eye (× 48). Some of the hemorrhage on the left has been removed in the fixing process, but the hemorrhage is seen to lift the internal limiting layer of the retina. The latter is continuous from intact retina to the area covering the hemorrhage. The large hump in the retina is probably an artifact. Armed Forces Institute of Pathology Acession No. 319751.

B, high power magnification (× 130) of *A*, showing the internal limiting membrane to be continuous from the intact retina to the "containing sac" for the subhyaloid hemorrhage. Armed Forces Institute of Pathology Accession No. 319751.

The past history had been essentially normal, except for frequent frontal headaches over the past two years; these had increased in severity during the pregnancy. She had received heavy-metal therapy in the 1930's and penicillin in 1948.

Physical Examination.—The patient was acutely ill and in coma, with labored respirations. She had definite signs of intracranial hemorrhage—elevated spinal-fluid pressure (300 mm.) and bloody spinal fluid. The blood pressure as recorded in the hospital was 190/130.

Ophthalmologic Examination.—The right eye was obviously exophthalmic and at the first ophthalmologic consultation showed conjunctival chemosis and subconjunctival hemorrhage on the right side. The pupils were round and equal and reacted to light.

The fundus of the right eye showed venous congestion and several small punctate hemorrhages. Papilledema was not thought to be present at this time. The fundus of the left eye showed a large (6 disk diameters), reddish-brown, elevated mass temporal to the disk, including the macular area. The mass was well circumscribed, and no vessels were visible on its surface. No other hemorrhage was noted in this eye. Papilledema was not thought to be present in the left eye.

Laboratory Tests.—The urine gave a 4+ reaction for albumin on all examinations. The urea nitrogen measured 15 mg. and the uric acid 6.6 mg. per 100 cc.

Course in Hospital.—The patient remained comatose. Owing to the severity of her condition, a Caesarean section was performed, with the use of local anesthesia, on the second hospital day, with delivery of a living boy, weighing 7 lb. 3 oz. (3,260 gm.). Immediately after delivery of the infant, the patient's respirations became slower, and her condition appeared to improve. The urinary output continued to be very low, however. She remained comatose and died on the fourth hospital day.

Autopsy.—Necropsy, performed within three hours after death, revealed pulmonary edema and bilateral renal infarction.

Brain: A small (6 to 7 mm.) berry aneurysm was observed in the roof of the third ventricle. This had ruptured, giving rise to the massive subarachnoid hemorrhage.

Eyes: Right eye: Removal of the right eye disclosed a large hemorrhage surrounding the optic nerve and apparently extending from the apex of the orbit. No blood was seen around the intracanalicular portion of the optic nerve.

Left eye: There was no exophthalmos or gross orbital hemorrhage. The portion of the optic nerve passing through the optic foramen did not contain blood.

Pathological Study.—The two eyes were sent to the Armed Forces Institute of Pathology for study. The pathological report (Accession No. 319751) follows.

Gross Examination: The specimens consist of a right and a left eye.

Right eye: The globe measures 23 by 25 mm. The eye is opened horizontally. Engorged vessels radiate from the slightly swollen optic disk. The macula is slightly swollen. The clear vitreous is normal in consistency, and the iris-lens diaphragm is in normal position.

Left eye: The globe measures 23 by 24 by 25 mm. The eye is opened horizontally. On the retinal surface is a flat brown discoloration, which extends from the optic disk into the macular and perimacular area (Fig. 1) and measures 7 by 11 mm. No evidence of retinal detachment is noted grossly.

Microscopic Study: Both eyes show moderate papilledema (Fig. 2). The right eye is otherwise not remarkable. In the left eye a large preretinal hemorrhage is present in the macular area on the temporal side (Fig. 3*A*). Adjacent to this are a few red blood cells beneath the retina (Fig. 3*B*). Small retinal hemorrhages and serous exudate are present in the outer plexiform layer on each side of the optic disk.

Diagnosis.—The diagnosis is bilateral papilledema, and retinal, preretinal, and subretinal hemorrhages in the left eye.

COMMENT

The generalization that a sudden, rapid rise in intracranial pressure is the cause of hyaloid and intraorbital hemorrhages has been accepted by all authors. The exact mechanism by which this rapid rise in intracranial pressure produces the subhyaloid hemorrhage and the concomitant exophthalmos has been debated, however.

Earlier writers have stated the belief that there was a direct connection between the subarachnoid spaces of the brain and the subarachnoid spaces surrounding the orbital portion of the optic nerve.[10] This would mean that in the present case the blood would have had to pass from the third to the fourth ventricle through the aqueduct of Sylvius, and then out of the fourth ventricle into the subarachnoid spaces of the brain by way of the medial foramen of Magendie and the two lateral foramina of Luschka. From here, the blood would have had to pass (still in the subarachnoid space) through the optic foramen to produce the phenomenon of stasis in the subarachnoid spaces surrounding the orbital portion of the optic nerve. Or, the blood may have dissected through the brain to the optic foramen and thence into the perineural subarachnoid spaces, or first along the fifth cranial nerve to the ciliary ganglion and thence down the intraorbital nerve sheaths. Some early work [11] and several good recent papers [12] indicate that the last mechanism is probably the one involved in some cases. It has been proved by pathological examination that none of these mechanisms was implicated in the present case.

The investigations by Liebreich,[1] Behr,[13] Ballantyne,[9b] and Walsh and Hedges,[14] with their beautiful pathologic demonstration, fully support the view that intraorbital and subhyaloid hemorrhages are caused by rupture of the veins within, and usually at the apex of, the orbit, and not by passage of intracranial blood through the optic foramen. The occurrence of subhyaloid hemorrhages after pneumoencephalography and in cases of rapidly increased intracranial pressure without intracranial hemorrhage also supports this view. It is likely that the initial rapid, sudden increase in intracranial pressure causes (by a combination of venous stasis and back pressure) the intraorbital and the subhyaloid hemorrhage to occur simultaneously.

Although part of the hemorrhage was lost in the technical processes incident to fixation and section, microscopic sections show that the subhyaloid hemorrhage was definitely under the internal limiting membrane, in agreement with the majority of authors. Rupture of the deep veins produces rounded, punctate intraretinal hemorrhage, while rupture of veins of the nerve fiber layer produces striate hemorrhage.

It is impossible to tell whether the 4+ degree of albuminuria was solely a manifestation of toxemia of pregnancy or whether it was in part the "transient massive albuminuria" described by Widal [15] in cases of subarachnoid hemorrhage.

We have recently had the privilege of seeing additional cases of subhyaloid hemorrhage due to subarachnoid hemorrhage from other sources. These subhya-

10. MacDonald.[2b] Riddoch and Goulden.[7b] Symonds.[8c]

11. Grimmer, W.: Ein Beitrag zur Entstehung des "traumatischen Sehnervenscheidenhämatoms," Ztschr. Augenh. **53**:41-54, 1924.

12. Wolff, E.: Anatomy of the Eye and Orbit, Ed. 3, Philadelphia, The Blakiston Company, 1948. Manschot, W. A.: Fundus Oculi in Subarachnoid Hemorrhage, Acta ophth. **22**:281-299, 1944; Correspondence to the Editor, Am. J. Ophth. **34**:1335-1336, 1951.

13. Behr, C.: Beitrag zur Anatomie und Klinik des septalen Gewebes und des Arterieneinbaus im Sehnervenstamm, von Graefes Arch. Ophth. **124**:227-267, 1935.

14. Walsh, F. B., and Hedges, T. R.: Optic Nerve Sheath Hemorrhages, Am. J. Ophth. **34**:509-527, 1951.

15. Widal, F.: Transient Massive Albuminuria, Presse méd. **2**:413, 1903.

loid hemorrhages were unilateral and on the side of the intracranial lesion. It seems, then, that the severity and bilaterality of the ocular lesion, as well as the lack of localization neurologically, speak clinically for a deep (intraventricular) and a midline lesion.

Certainly, the diagnosis of a ruptured intraventricular aneurysm is difficult to make ante mortem, but at least when one sees sudden exophthalmos and contralateral subhyaloid hemorrhage, or any combination of these two, without localizing neurologic signs in a semicomatose or comatose patient, one should keep in mind the rupture of an intraventricular aneurysm.

SUMMARY

A case of subhyaloid hemorrhage in one eye and of exophthalmos of the other due to the rupture of an intraventricular (third-ventricle) berry aneurysm in a woman aged 33 during toxemia of pregnancy is presented. The case appears to be unique in the literature.

The predominant prodromal symptom was headache.

Pathological examination of the eyes showed the hemorrhage to be contained between the internal limiting membrane of the retina and the nerve fiber layer.

Gallinger Municipal Hospital (Dr. Bisland).

844 Ave. C, Bayonne, N. J. (Dr. Topilow).

The scientific and technical personnel of the Armed Forces Institute of Pathology aided in this study.

STUDIES IN EXPERIMENTAL OCULAR TUBERCULOSIS

XVI. Effect of Corticotropin, Cortisone, and Compound F on Development of Experimental Ocular Tuberculosis in Immune-Allergic and Normal Rabbit

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AND
RONALD M. WOOD, Ph.D.
BALTIMORE

IN A PREVIOUS communication [1] it was pointed out that the parenteral injection of corticotropin (ACTH) and cortisone in immune-allergic rabbits with secondary ocular tuberculosis, produced by injection of tubercle bacilli into the anterior chamber, somewhat altered the course of the disease in such eyes. It was found that the administration of corticotropin and cortisone to these animals, prior to the parenteral injection of tuberculin, blocked the focal ocular reaction which was constantly observed in the untreated controls. It was further found that the continued use of cortisone for a three-week period in such animals appeared to control the inflammatory phase of the ocular tuberculosis, leaving the peculiar picture of uninflamed eyes with active tubercles in the iris or cornea.

In this experiment it was not clear whether this suppression of the inflammation had any effect on the actual progress of the tuberculous process in the eyes. This point was difficult to judge because, first, the course of tuberculosis in the eyes of immune-allergic rabbits is a restrained one; second, the severity of the restrained disease may vary considerably in individual rabbits, depending probably upon the degree of immunity present, and, third, the cortisone treatment is of relatively short duration. Lurie and his associates [2] have recently reported that the continued administration of cortisone in rabbits may markedly and fundamentally affect the pathogenesis of tuberculosis produced by inhalation of tubercle bacilli. Treatment with cortisone increased the engrafting of bacilli in the lungs and also retarded the dissemination of the disease in the experimental animal. The tubercles in the treated rabbits were sharply delineated, with caseous foci swarming with bacilli. These investigators believed that the hormone, instead of increasing the destruction of the bacilli, probably increased their number in the lesions, owing to increased phagocytic activity of the reticuloendothelial cells and the alveolar macrophages, with retention of the bacilli in the alveoli. In January, 1951, the National Tuberculosis Association issued a warning [3] against the use of corticotropin and cortisone

This investigation was supported by a research grant from the Experimental Therapeutics Section, National Institutes of Health, United States Public Health Service.

1. Woods, A. C., and Wood, R. M.: Action of ACTH and Cortisone on Experimental Ocular Inflammation, Bull. Johns Hopkins Hosp. **87**:505 (Nov.) 1950.

2. Lurie, M. B., and others: Constitutional Factors in Resistance to Infection: Effect of Cortisone in Pathogenesis of Tuberculosis, Science **113**:234 (March 2) 1951.

3. ATS Warns on Tuberculosis: Urges Tests, Bull. of Nat. Tuberc. A. **37**:4 (Jan.) 1951.

in treatment of tuberculous patients until further investigation might show it to be safe in specific instances.

It is probably true that the course of tuberculosis produced in the lung by inhalation of bacilli may be quite different from that produced in the eye by the injection of bacilli into the anterior chamber. In the eye the local disease is, of necessity, circumscribed in a tight corneoscleral envelope, and it is as yet undetermined whether continued treatment with the adrenocortical hormones may have a beneficial or an adverse effect. The control of the inflammatory phase of a bacterial disease might conceivably lessen the dissemination of the organisms throughout the eye and make any present or developing immunity more effective. On the other hand, it is equally possible that the use of corticotropin or cortisone may so alter the natural pattern of a disease process that the normal factors of resistance are disturbed and the acquisition of immunity may be inhibited. It is also possible that the use of these agents may inhibit or diminish the fibroblastic reaction in the eye which is responsible for the encapsulation of the tuberculous lesion and thus promote dissemination of the bacilli in the eye. It is further possible that the continued use of cortisone may damage the host's own adrenal cortex to the extent the animal is left defenseless when treatment is terminated.

Since cortisone has been used somewhat extensively by ophthalmologists in the treatment of granulomatous uveitis, much of which must be tuberculous, and since there is considerable theoretical and some experimental evidence at hand that the adrenocortical hormones may ultimately prove to have anything but a beneficial action in tuberculosis, the question of their action in ocular tuberculosis is urgently in need of exploration. The experiments here reported were therefore undertaken to determine just what effect, if any, continued treatment with the adrenocortical hormones would have on developing ocular tuberculosis in the normal and in the immune-allergic animal.

Primarily, it must be emphasized that ocular tuberculosis which follows the injection of tubercle bacilli into the anterior chamber runs quite a different course in the normal (nonimmune) animal than it does in the immune-allergic animal. In the normal animal there is a minimal immediate reaction to the injection of the bacilli. After a short incubation period, hard tubercles, with a moderate inflammatory reaction, develop in the iris and cornea. As the disease progresses a local reactivity to tuberculin develops, and the inflammation becomes acute and violent. The tubercles soften; necrosis and caseation occur; the eyes go into buphthalmos and frequently rupture in four to six weeks. Ocular tuberculosis in the normal rabbit, therefore, presents a severe test of the capability of an agent either to control inflammation or to alter the course of the disease.

On the other hand, it requires a larger dose of bacilli to produce lesions in the eye of an immune-allergic rabbit than in the eye of a normal rabbit. When an appropriately larger dose is given 24 to 48 hours after the injection of the bacilli in the anterior chamber, there is a sharp inflammatory reaction—the typical picture of nongranulomatous iritis. This initial reaction is a bacterial hypersensitivity reaction produced in a hypersensitive animal by the tuberculoprotein in the inoculum. It usually fades in from two to seven days, depending on the sensitivity of the rabbits receiving the injection. Thereafter there is an incubation period of one to three weeks. Low-grade inflammation then develops, with tubercle formation in the iris

and cornea. The disease now runs a restrained course and, after several months, finally heals, leaving more or less residual scarring and organic changes, the degree depending on the severity of the disease. Caseation and rupture of the globe are extremely rare except after injection of a heavy dose of bacilli in an extremely hypersensitive rabbit. The disease in immune-allergic rabbits, therefore, gives the observer an opportunity both to determine the effect of an agent on the control of the initial allergic reaction to the tuberculoprotein in the inoculum and also to study any effect the agent may have on a disease restrained by immunity resulting from the prior systemic infection. It is not an unduly severe test of the capability of the agent under examination.

In the experiments here reported, the effect of the adrenocortical hormones on ocular tuberculosis was studied both in the normal and in the immune-allergic rabbit. Experiments 1 and 3 were first run synchronously. Experiments 2 and 4, which are essentially more elaborate repetitions of Experiments 1 and 3, were run after the completion of the first experiments. For the sake of clarity, they are here reported out of chronological order.

I. EFFECT OF ADRENOCORTICAL HORMONES ON OCULAR TUBERCULOSIS IN THE NORMAL RABBIT

EXPERIMENT 1.—*Technique.*—On Nov. 18, 1950, 19 normal rabbits of either sex, but of the same breed as those used in former experiments, were inoculated in the anterior chamber of the right eye with 0.1 cc. of a suspension of living tubercle bacilli so diluted it contained 5 bacilli to each oil-immersion field. These rabbits were divided into three groups. Group 1 (six rabbits) was left untreated, as a control. Group 2 (seven rabbits) was treated with cortisone, 10 mg. a day, in two divided doses. Treatment was begun four days prior to inoculation of the anterior chamber and was continued throughout the life of the experiment (46 days). Group 3 was divided into two subgroups. Subgroup 3A (three rabbits) was treated with beef corticotropin, 10 mg. a day in acthar® vehicle, in two divided doses. Subgroup 3B (three rabbits) was treated with pork, corticotropin. Treatment was begun four days prior to the anterior-chamber inoculation and was continued for 46 days, during the life of the experiment.

After inoculation of the eyes, all rabbits, Groups 1, 2, and 3, were examined clinically at intervals of from one to seven days as the experiment progressed, and the degree of tuberculous activity or inflammation in the eyes was evaluated on a numerical scale, as in former experiments, and charted graphically. Thus, there resulted a chart showing the course of the disease in the various groups and permitting a comparison of the treated animals and the untreated controls.

Clinical Results.—The results are shown graphically in Figure 1. There was a negligible reaction to the injection of the bacilli in the anterior chamber. There was then a latent period of approximately 15 days before the eyes began to show inflammation and small tubercles. By the 20th day the tubercles were well developed. Thereafter a rapid severe ocular tuberculosis devoloped, with violent acute inflammation, buphthalmos, necrosis, and caseation, and by the 34th day a large number of globes had ruptured.

There was no discernible difference between the control (Group 1) and the treated rabbits (Groups 2 and 3) either in the inflammatory picture or in the progress of the tuberculous disease. All rabbits treated with cortisone lived throughout the experiment. Two rabbits treated with pork corticotropin died, one after four days' treatment, and one after 14 days' treatment. The remaining rabbit treated with pork corticotropin reacted in a manner exactly similar to that of the three rabbits treated with beef corticotropin.

Histological examination of the eyes enucleated after completion of the experiment showed no essential difference between the controls and the treated animals. All eyes showed the picture previously described, with advanced tuberculous infiltration and soft, spreading tubercles, with marked tissue necrosis and caseation.

EXPERIMENT 2.—*Technique.*—On April 3, 1951, 24 normal rabbits were inoculated in the anterior chamber of the right eye with a suspension of living, virulent human tubercle bacilli so diluted it contained 2 organisms per oil-immersion field. The rabbits were divided into four groups. Group 1 (six rabbits) was left untreated as a control. Group 2 (six rabbits) was treated with cortisone, 5 mg. a day in one dose; Group 3 (six rabbits) was treated with Compound F (17-hydroxycorticosterone-21-acetate),[4] 5 mg. a day in one dose. Group 4 (three rabbits) was treated with pork corticotropin, 5 mg. a day in acthar® vehicle, in two divided doses. Group 5 (three rabbits) received similar inoculations of tubercle bacilli in the anterior chamber of both eyes, and the rabbits were thereafter treated with local instillations of cortisone ointment (25 mg. per gram of base) in the conjunctival sac of both eyes twice a day. In Groups 2, 3, and 4 treatment with the various agents was commenced eight days prior to inoculation of the eyes. Treatment was continued in Group 2 for a period of 53 days, and in all survivors of Groups 3, 4, and 5 for a 56-day period.

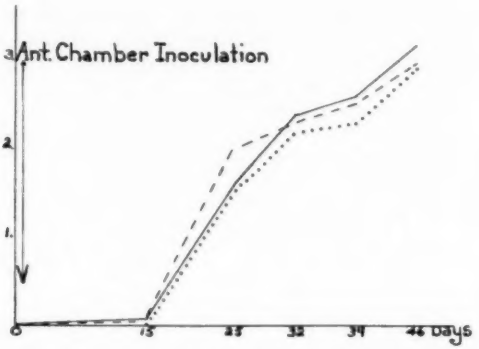

Fig. 1.—Effect of cortisone (broken line) and corticotropin (dotted line) on development of tuberculous lesions, in the eyes of normal rabbits (Experiment 1). Values for controls are shown by solid lines.

It should be noted that in this experiment the inoculum of tubercle bacilli used was two-fifths that used in Experiment 1, and the dose of corticotropin and cortisone was one-half that used in the first experiment. The reasons for these changes in inoculum and dosage were, respectively, an effort to produce a less extensive disease, and so to provide a less severe test for the efficacy of these agents in the normal rabbit, and to lessen a possible toxic action of the agents and so permit a more extended period of observation. Further, this experiment contained two additional groups, one treated with Compound F and one treated topically with cortisone ointment in the conjunctival sac.

The rabbits were examined clinically at intervals of from one to seven days during the period of treatment. Thereafter all survivors were examined every seven days for an additional five weeks, and the corticotropin-treated rabbits, for an additional four weeks. The results were charted as in the previous experiment.

Clinical Results.—A. Eyes of Controls and Parenterally Treated Rabbits: The course of the ocular tuberculosis in Groups 1, 2, 3, and 4 (untreated controls and

4. The Compound F used in this experiment was supplied by Merck & Company, Inc., Rahway, N. J.

cortisone-treated, Compound-F-treated, and corticotropin-treated rabbits, respectively) is shown in Figure 2. Fourteen days after the inoculation of the anterior chamber, the eyes of all animals exhibited an ocular tuberculosis identical in character and course with that in the normal rabbits in Experiment 1. There was no difference of statistical significance in the character or course of the disease in the controls and in the treated rabbits during the period of treatment. In all rabbits the ocular disease, once started, ran a malignant course, characterized by rapidly developing inflammation, necrosis, and caseation, with rupture of approximately 50% of all eyes by the 45th to the 50th day after inoculation. There was certainly no clinical evidence that cortisone, Compound F, or corticotropin retarded the progression of the tuberculous ocular disease in these normal animals.

After treatment was stopped, on the 56th day, the surviving animals were kept under observation for a further period of five weeks to determine, if possible,

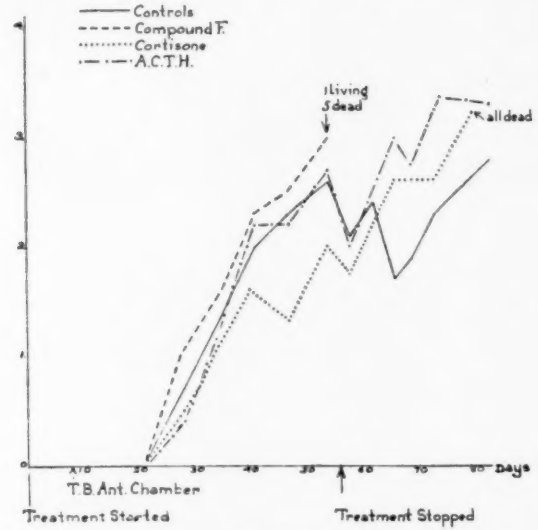

Fig. 2.—Effect of systemic treatment with cortisone, corticotropin, and Compound F on the development of tuberculous lesions in the eyes of normal rabbits (Experiment 2).

whether any difference in the disease developed in the treated animals as compared with that in the controls after cessation of treatment. At this time, there were two survivors in the cortisone-treated group, one survivor in the Compound-F-treated group, two in the corticotropin-treated group, and two in the group receiving topical cortisone treatment. As shown in Figure 2, there was a definite increase in the severity of the picture in all the surviving treated animals, as compared with that in the controls. Figure 3*A* and *B* show, respectively, the appearance on the 90th day (five weeks after termination of treatment) of the eyes of normal rabbits treated by parenteral injection of cortisone and Compound F, in contrast with that of the eye of an untreated control on the same date (Fig. 3*C*). However, the number of survivors was so small, and the disease of such severity in both the treated and the control animals, that no really valid conclusions could be drawn on this point.

B. Eyes of Rabbits Treated Topically with Cortisone: The course of the ocular disease in the six eyes of three rabbits treated by topical application of cortisone ointment (25 mg. per gram of base), as compared with that in the untreated controls, is shown in Figure 4. In both the treated rabbits and the untreated controls, the ocular inflammation began on the 21st day after inoculation. In the two groups the disease pursued an identical course until treatment was terminated. One rabbit died on the 52d day of treatment. The remaining two animals were kept under observation for a further period of five weeks after treatment was terminated. During this period the disease in the previously treated eyes became much severer than in the untreated controls. This difference, while of doubtful statistical sig-

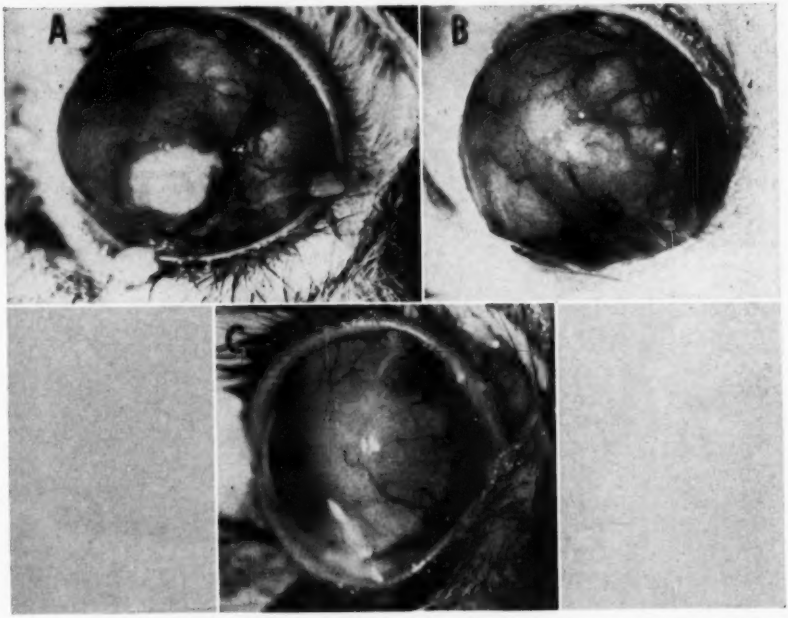

Fig. 3.—*A*, external appearance of eye of normal rabbit treated with cortisone, 30 days after termination of treatment, illustrating accentuation of inflammation. *B*, external appearance of eye of normal rabbit, treated with Compound F, 30 days after termination of treatment, illustrating accentuation of disease. *C*, external appearance of eye of untreated normal control, 30 days after inoculation.

nificance on account of the small number of animals, may well represent a counterpart of the rebound phenomenon observed in immune-allergic rabbits and hereafter reported.

Certainly, the topical use of cortisone ointment in the eyes of normal rabbits with ocular tuberculosis, produced by injection of living bacilli into the anterior chamber, had no deterrent action on the course or character of the disease. On the contrary, after the topical treatment was terminated the eyes appeared to be more susceptible to a spreading infection than did the controls.

C. Mortality: In the six control rabbits there was one death from an intercurrent cage infection, which occurred on the 50th day after inoculation. Autopsy did not reveal any spread of the tuberculous disease beyond the site of inoculation in the eye.

In Group 2, treated with cortisone, four deaths occurred between the 53d and the 56th day of treatment, there being only two survivors at the end of the experiment, the mortality under treatment being 66%. The survivors were killed after a further period of five weeks' observation.

In Group 3, treated with Compound F, there were five deaths, between the 55th and the 58th day. The remaining rabbit was killed at the end of the period of observation, on the 90th day. Thus, in this group there was a total mortality of 84%, the animals dying either while under treatment or within two days after treatment was terminated.

In Group 4, treated with corticotropin, there was one death only, on the 27th day of treatment.

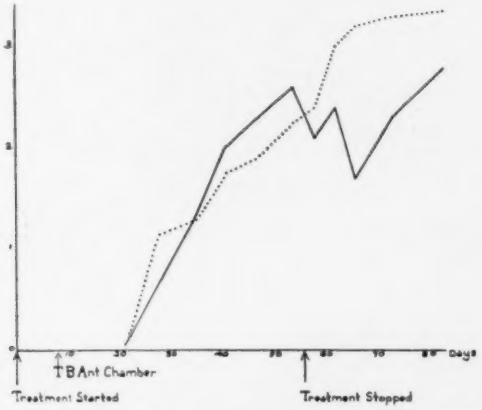

Fig. 4.—Course of tuberculosis in six eyes of three normal rabbits treated by instillation of cortisone ointment in conjunctival sac (dotted line), contrasted with course of disease in untreated controls (solid line).

In Group 5, treated by topical application of cortisone, there was, again, one death only, on the 52d day of treatment, from an incidental infection of the upper respiratory tract.

D. Weight Variation: In Group 1, the untreated controls, there was a definite gain in weight during the course of the experiment, the average weight on April 6, at the beginning of the experiment, being 2.9 kg., and on June 6, after treatment was terminated, 3.4 kg.

In Group 2, treated with cortisone, the average weight of the animals at the beginning of the experiment was 2.9 kg. On May 5, when all animals were still living, the average weight was 2.8 kg., and on June 4, after treatment was terminated, the average weight of the two survivors was 2.6 kg.

In Group 3, treated with Compound F, there was a definite loss of weight under treatment. The average weight at the beginning of treatment was 2.7 kg. On

May 7, when all animals were still living, the average weight was 2.3 kg., and on June 4 the lone survivor showed a loss of weight of from 2.6 to 2.2 kg.

In Group 4, treated with corticotropin, there was a gain in weight similar to that shown by the untreated controls, from an average of 2.4 kg., at the beginning of the experiment, to 2.8 kg., when treatment was terminated.

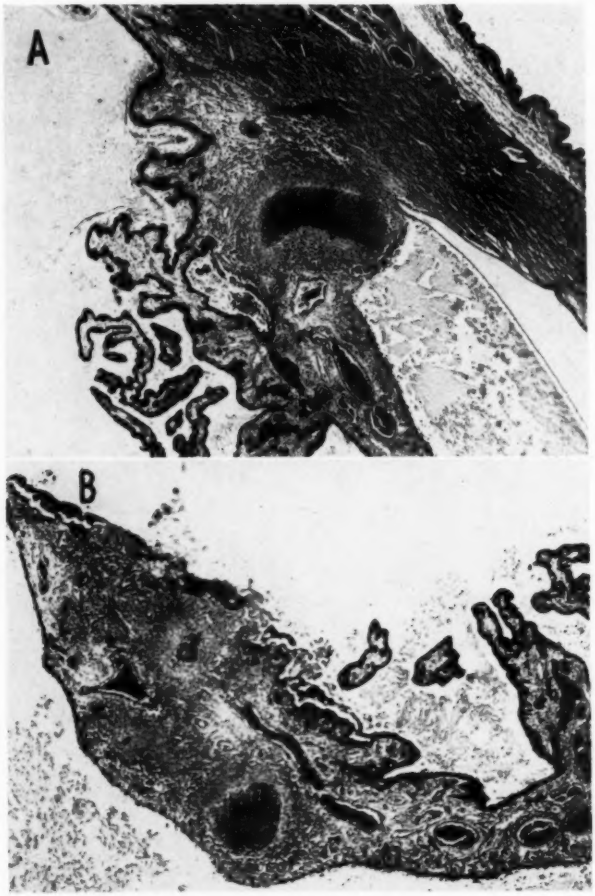

Fig. 5.—*A*, maximum tuberculous disease of ciliary body in untreated normal control (× 30). *B*, maximum tuberculous disease of iris in untreated normal control (× 34).

In Group 5, treated topically with cortisone, there was a gain in weight similar to that shown by the controls and the corticotropin-treated rabbits, from an average weight of 2.7 kg., at the beginning of the experiment, to 3.1 kg., when treatment was terminated.[5]

5. The significance of the high mortality and loss of weight in the rabbits treated with cortisone and Compound F will be discussed in a subsequent communication.

Histological Studies.—A. Eye of Controls: The control eyes showed the usual picture of tuberculosis in the normal rabbit, where the course of the disease is unrestrained by any preinduced immunity. There were large massive tubercles in the ciliary body with caseous centers but with some tendency to encapsulation. Large, spreading tubercles were present throughout the edematous iris, with minor to massive tuberculosis of the cornea, the disease process extending forward into the cornea from the root of the iris. As was before observed in the normal rabbit, there was little tendency for the disease to extend backward to the posterior ocular segment. Figure 5*A* illustrates the maximum reaction in the ciliary body in an unruptured eye of an untreated control rabbit, and Figure 5*B*, the maximum reaction in the iris.

B. Eyes of Rabbits Treated Parenterally with Cortisone: The four rabbits dying between the 53d and the 56th day, just at the end of treatment, showed

Fig. 6.—Extension of tuberculous disease in ciliary body of normal rabbit treated by parenteral injection of cortisone.

similar pictures. There were large tubercles with caseous centers in the ciliary body and early extension of the disease back into the choroid (Fig. 6). The irides showed a picture similar to that of the untreated controls. There was little or no evidence of encapsulation or fibrosis.

The two rabbits killed after a 5-week period of post-treatment observation showed a marked accentuation of the tuberculous disease. In one rabbit the eye showed advanced buphthalmos and was at the point of rupture. The cornea was involved, and there was extension of the infiltration to the posterior chamber, with hemorrhage, necrosis, and caseation. The diseased eye of the second rabbit had ruptured. Histological examination showed that the whole anterior segment was virtually replaced by a mass of necrotic tuberculous granulation tissue, with obliteration of all normal landmarks (Fig. 7*A*). There was, however, only slight extension to the choroid. The degree of tuberculosis in these two animals was greatly in excess of that shown by any of the controls and, likewise, was much severer than

that shown by the cortisone-treated rabbits dying while still under treatment. There was no evidence whatsoever of any encapsulation of the lesions or of fibrosis in either of these two eyes.

C. Eyes of Corticotropin-Treated Rabbits: The rabbit dying on the 27th day of treatment showed no clinical evidence of ocular tuberculosis at the time of death, and likewise showed no histological evidence of the disease, the eye being devoid

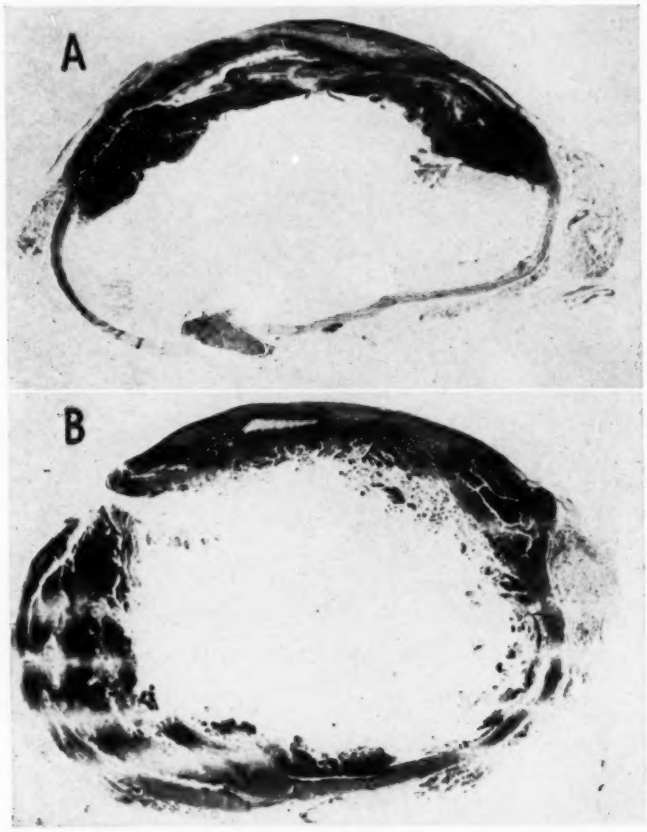

Fig. 7.—*A*, accentuation of tuberculosis with involvement of entire anterior segment in eye of normal rabbit after termination of parenteral treatment with cortisone. *B*, extreme ocular tuberculosis in normal rabbit treated with corticotropin, 34 days after cessation of treatment.

of even early lesions. The two animals killed after the five-week period of post-treatment observation showed advanced disease. The eye of one rabbit had not ruptured and histologically showed massive tuberculous disease, limited almost entirely to the anterior ocular segment. The eye of the second rabbit had ruptured one week prior to the time it was killed. This eye showed extensive, massive disease, not only involving the anterior ocular segment but extending backward, involv-

ing the entire choroid and retina, obliterating all normal landmarks, and invading the sclera (Fig. 7*B*). This was probably the most extensive ocular involvement shown by any of the animals in this experiment.

D. Eyes of Compound-F-Treated Rabbits: All rabbits treated with Compound F showed a histological picture of ocular tuberculosis much more advanced than in the controls. There were huge caseous tubercles in the ciliary body (Fig. 8*A*),

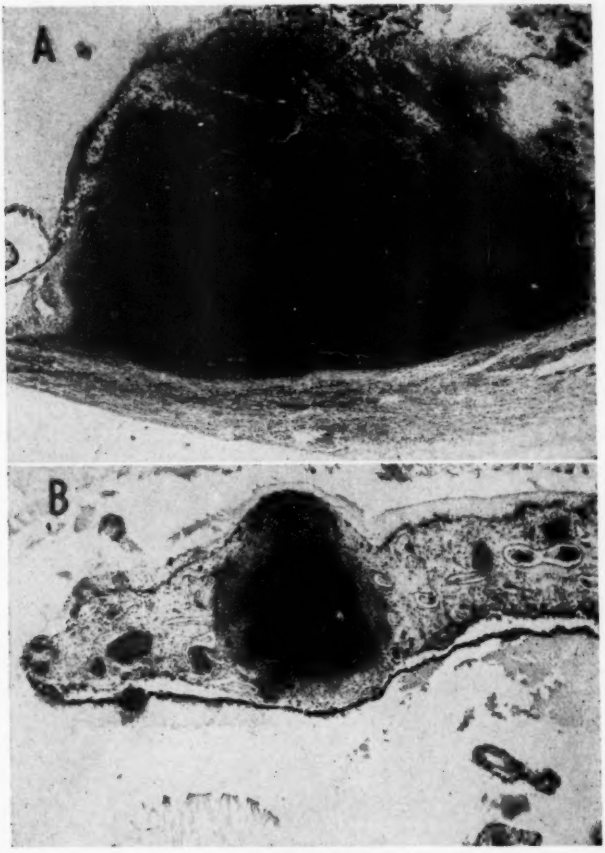

Fig. 8.—*A*, maximum tuberculous disease of ciliary body in normal rabbit treated with Compound F (× 30). Compare with Figure 3*C*. *B*, maximum disease of iris in normal rabbit treated with Compound F (× 34).

much larger than those observed in either controls or cortisone- or corticotropin-treated animals. There were similar large caseous tubercles in the iris (Fig. 8*B*) and pronounced extension of the disease to the posterior segment, involving both the choroid and the retina (Fig. 9*A*). Especially interesting were a number of small caseous tubercles lying free in the vitreous (Fig. 9*B*). These tubercles apparently

had originated in the internal layers of the retina and, breaking loose, had floated forward in the vitreous. Far from inhibiting the disease process, treatment with Compound F accelerated the spread and intensity of the disease. The one survivor, killed 34 days after cessation of treatment, showed advanced caseating tuberculosis of the cornea, ciliary body, and iris, with some extension backward into the choroid.

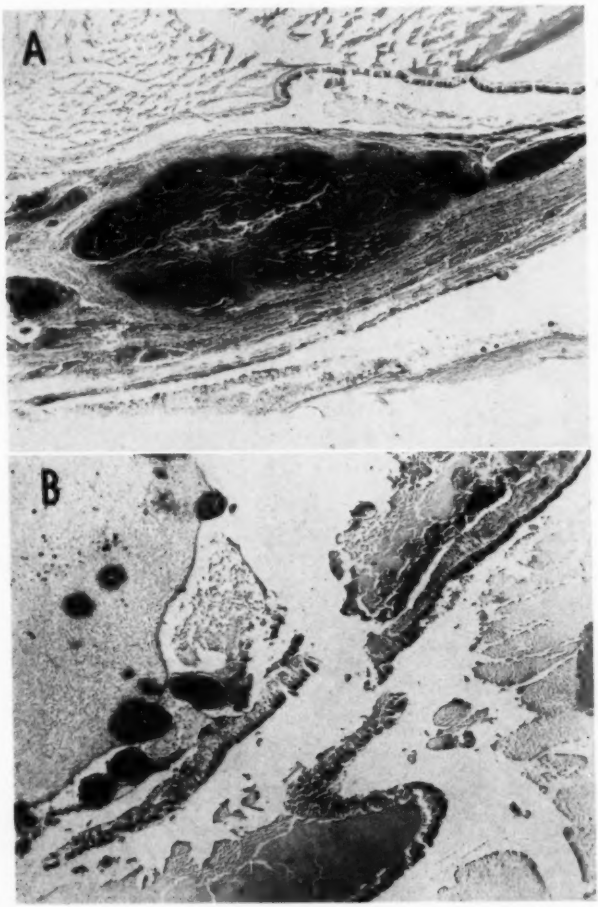

Fig. 9.—*A*, extension of tuberculous disease from ciliary body back to choroid in normal rabbit treated with Compound F. *B*, free tubercles in vitreous in normal rabbit treated with Compound F.

E. Eyes of Rabbits Treated Topically with Cortisone: The rabbit dying on the 52d day of treatment showed a histological picture quite similar to that of the controls, with large caseous tubercles in the ciliary body and iris and early involvement of the anterior choroid.

The two animals killed after the four-week period of post-treatment observation showed a greatly advanced picture. In one rabbit the right eye was undergoing buphthalmos but had not ruptured. The left eye had ruptured. Histologically, the unruptured right eye showed massive tuberculous infiltration involving the entire anterior ocular segment and extending well back into the choroid, but leaving the extreme posterior segment uninvolved. The ruptured left eye showed even more extensive involvement of the anterior segment, obliterating all normal markings, but again leaving the extreme posterior portion free (Fig. 10). The second of these rabbits showed a similar, but possibly slightly less extensive, picture.

F. Tissue of Control Rabbits: Autopsies on the untreated controls revealed no significant gross lesions (except in the eyes). Histological examination of the various tissues showed an occasional hard tubercle in the lung, spleen and liver. The kidneys and adrenals were uniformly clear in all the control animals. In several of the controls no lesions of any kind could be found in the lungs, spleen, or kidneys. Such tubercles as were found showed little or no evidence of necrosis or caseation.

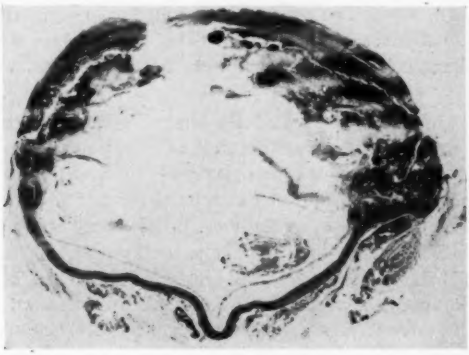

Fig. 10.—Extensive tuberculosis in ruptured left eye of normal rabbit treated by topical application of cortisone, 34 days after termination of treatment.

G. Tissues of Rabbits Treated Parenterally with Cortisone: Five of the six rabbits treated parenterally with cortisone died between the 53d and the 56th day, while still under treatment, and in all autopsy showed no gross pathologic changes. In one of these animals there was so much postmortem change that the histological examination was unsatisfactory. The liver showed extreme fatty changes, and a few tubercles were identified. The adrenals were small but showed no microscopic change. In the remaining three animals numerous tubercles were scattered through the lungs, liver, spleen, and, in one animal, the kidney. Strangely, there was no apparent excess storage of glycogen in the liver of any of the rabbits. One animal showed early signs of the specific changes in the kidney which have been described by Rich and his co-workers[6] after administration of cortisone—dilatation and hyalinization of the capillaries of the glomeruli, with blood and casts in the tubules.

6. Berthrong, M.; Rich, A. R., and Bennett, I. L.: Effect of Cortisone on the Experimental Cardio-Vascular and Renal Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **87**:549 (Nov.) 1950.

One rabbit showed more advanced renal changes, with hyaline masses in the glomeruli and occasionally a completely hyalinized glomerulus.

In the two rabbits killed after the five-week period of observation, gross examination showed occasional scattered tubercles over the surface of the kidney, liver, and intestine. In one animal histological examination showed tubercles on the capsule of the liver, and in the second animal, what might be atypical tuberculous changes. This animal, however, showed also the typical changes of incidental coccidiosis. There were no specific renal changes. The adrenals were normal in size and structure.

H. Tissues of Corticotropin-Treated Rabbits: The corticotropin-treated rabbit that died on the 27th day of treatment showed chronic pneumonitis, the tissues otherwise showing no change on gross or microscopic examination except for postmortem autolysis.

One of the rabbits killed five weeks after termination of treatment showed advanced tuberculosis of the lung and spleen. The liver presented many giant cells of old, dissolved tubercles. The kidneys were normal. The adrenals were normal except for the loss of lipid. The second rabbit killed after termination of treatment showed an occasional tubercle in the lung. The other tissues were normal. The adrenals revealed some loss of lipid but were normal in size, weighing 375 and 382 mg.

I. Tissues of Compound-F-Treated Rabbits: The animals treated with Compound F showed the most extensive tuberculosis of any of the several groups. On autopsy, gross pulmonary changes were observed in three of the six animals; miliary tubercles were present in the kidneys of all animals, and in three of the six animals gross tubercles were scattered over the liver. Microscopic study revealed that the lungs were involved in four of the six rabbits, the liver and kidneys of all animals were literally riddled with tubercles, and the spleen was involved in five of the rabbits. In three animals the adrenals were normal. In two animals there was loss of lipid, and in one there were a number of miliary tubercles.

The most interesting lesion found in this group of rabbits was aneursymal dilatation of the capillaries of the glomeruli, with secondary hyalinization and blood in the tubules. This change was present in four of the six treated rabbits. The change was exactly similar to that described by Rich and his associates in cortisone-treated animals, a change which, as he pointed out, resembles that described by Kimmelstichl and Wilson in diabetes.

J. Tissues of Rabbits Treated Topically with Cortisone: Only one of the rabbits treated by topical application of cortisone showed macroscopic changes on autopsy. These consisted of tubercles in the lungs and on the surface of the kidney. On histological study, two of the three animals showed tubercles in the lungs; one, tubercles in the kidney; another, tubercles in the liver, and the third, scattered tubercles in the spleen. The changes noted were slightly more advanced than those in the controls. There were no capillary aneurysms in the glomeruli of the kidney.

II. EFFECT OF ADRENOCORTICAL HORMONES ON OCULAR TUBERCULOSIS IN THE IMMUNE-ALLERGIC RABBIT

EXPERIMENT 3.—*Technique.*—On Dec. 22, 1949, a large series of rabbits were inoculated in the groin with 0.25 cc. of a six week-old culture of human tubercle bacilli. On Nov. 14, 1950, 19 of these animals were tested for sensitivity by the intracutaneous injection of 0.1 cc. of

second-strength purified protein derivative of tuberculin U. S. P. All rabbits gave positive reactions, 13 reacting with an area of erythema of 10 mm. or more and six with reaction areas of from 5 to 10 mm. The rabbits were then divided into three groups on the basis of equal cutaneous sensitivity. Group 1 (six rabbits) was left untreated as a control; Group 2 (six rabbits) was treated with cortisone, 10 mg. a day, in divided doses, and Group 3 was divided into subgroups A and B of three rabbits each. Subgroup A was treated with beef corticotropin, and subgroup B, with pork corticotropin, 10 mg. a day, in divided doses. The treatment in both groups (groups 2 and 3) was begun four days prior to inoculation of the eyes and was continued for a 60-day period after inoculation. On Nov. 18, 1950, the anterior chamber of the right eye of all rabbits was inoculated with a 0.1 cc. of a suspension of living, virulent tubercle bacilli so diluted it contained 10 organisms per oil-immersion field when a 2-mm. loopful was spread over an area of 1 sq. cm.

Clinical Results.—A. Controls: The results of this experiment are shown in Figure 11 and may be summarized as follows: Within 24 to 48 hours after the injection of tubercle bacilli into the anterior chamber, all untreated controls showed a sharp inflammatory reaction in the injected eyes—the focal reaction to the tuberculoprotein in the inoculum. This reaction partially faded over the following week, and about the 15th day after inoculation the eyes began to show a low-grade,

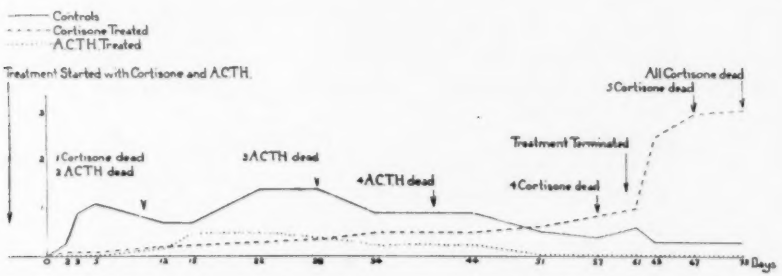

Fig. 11.—Effect of parenterally administered cortisone and corticotropin on course of ocular tuberculosis in immune-allergic rabbits (Experiment 3).

restrained tuberculosis. The active tuberculous disease increased for about two weeks, remained moderately active for another two weeks, and then began to wane. At the end of the experiment the average intensity of disease in the controls was 0.3, the eyes of three animals being entirely inactive and those of three showing moderate persisting inflammation. There was no evidence of buphthalmos, necrosis, or caseation. There were no deaths in the control group. The degree of tuberculous disease in these eyes was somewhat less than that shown by other groups of immune-allergic rabbits reported in previous experiments. The probable reason for this diminished reaction was the long interval between the systemic injection and the injection into the anterior chamber. In the animals used in this experiment this period was approximately one year, as opposed to the usual interval of three to six months. During this longer period the animals had apparently acquired an increased resistance to reinfection.

B. Cortisone-Treated Rabbits: The results in the cortisone-treated group were radically different. Primarily, the rabbits did not tolerate well the 10-mg. daily dose of cortisone over the prolonged period. One rabbit died on the 10th day after

inoculation (14th day after treatment); three died between the 51st and the 57th day; one, on the 64th day, and the last, on the 72d day.

Treatment with cortisone for four days prior to the anterior-chamber inoculation completely blocked the focal reaction due to tuberculoprotein in the inoculum shown by the untreated controls. This confirmed the results of the previous experiments, already reported. Thereafter after injection the eyes showed a low-grade tuberculosis, which at first was distinctly less severe that that shown by the controls. By the

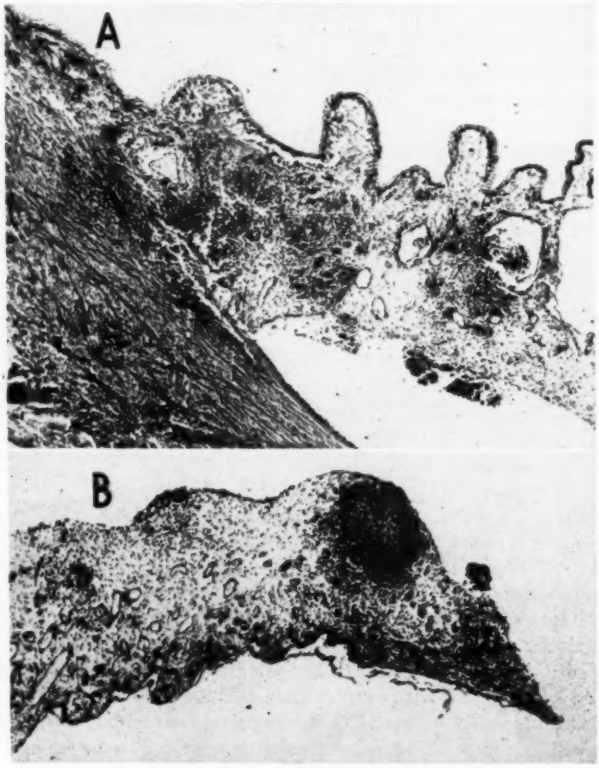

Fig. 12.—*A*, discrete tubercles throughout iris and ciliary body in cortisone-treated immune-allergic rabbit dying on 52d day of treatment. *B*, tubercles of iris with caseous center in cortisone-treated immune-allergic rabbit dying on 52d day of treatment.

50th day of treatment, however, there was little difference in the two groups, and at the conclusion of treatment, when there were only two survivors in the treated group, the two groups were essentially the same.

Although the experimental rabbits surviving after termination of treatment were few, the course of the disease in the survivors, nevertheless, was most interesting. Immediately after discontinuation of cortisone, on the 60th day, the two survivors showed a sudden and marked increase in the inflammation and rapid spread of the

tuberculosis, with outbreak of a fresh crop of tubercles in the iris. One of these rabbits died on the 67th day. The disease in the lone survivor continued to increase in severity for the following week, and the animal died on the 72d day. This rebound phenomenon was somewhat suggestive of the altered reaction to Treponema infection reported by Turner after termination of cortisone therapy.[7]

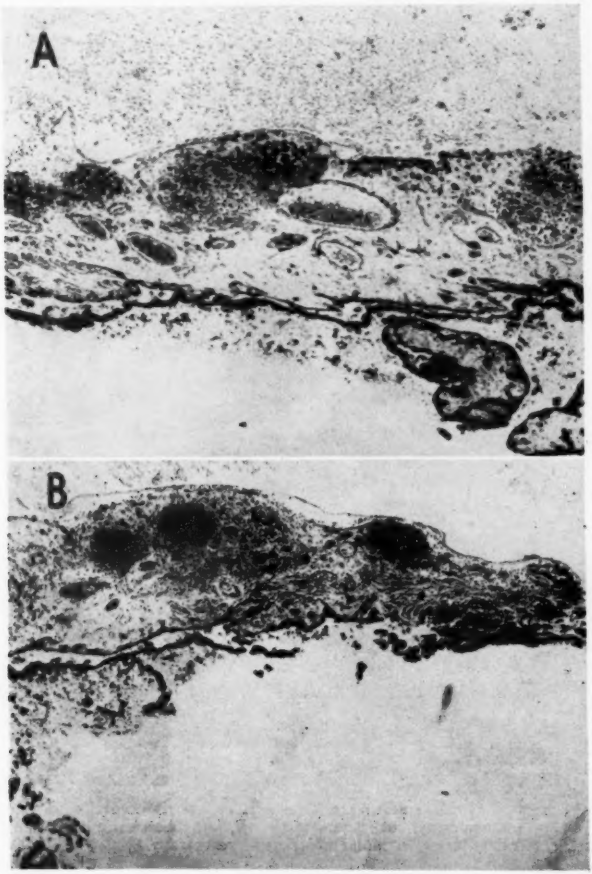

Fig. 13.—*A*, soft, early tubercles with no evidence of fibrosis in cortisone-treated immune-allergic rabbit dying on 57th day of treatment. *B*, soft tubercles, with no evidence of fibrosis in cortisone-treated immune-allergic rabbit dying on the 57th day.

C. Corticotropin-Treated Rabbits: All rabbits treated with corticotropin, of both pork and beef derivation, showed complete suppression of the focal reaction to the tuberculin in the inoculum shown by the controls. Thereafter, beginning about

7. Turner, T. B., and Hollander, D. H.: Cortisone in Experimental Syphilis, Bull. Johns Hopkins Hosp. **87**:505 (Nov.) 1950.

the 12th day, the treated rabbits exhibited minimal signs of inflammation and ocular tuberculosis. Between the 8th and the 36th day of treatment there were four deaths in the corticotropin-treated rabbits. By the 51st day all evidences of active ocular inflammation had disappeared in the two surviving animals, and when treatment was stopped on the 60th day, the eyes were entirely inactive. One of these animals died on the 67th day, and the last was diverted for another experiment on the

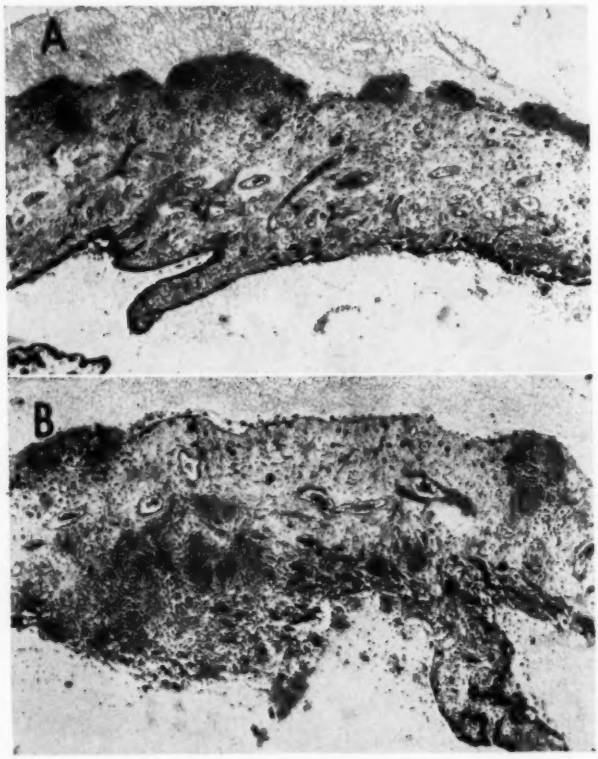

Fig. 14.—*A*, rows of fresh, soft tubercles on surface of iris occurring in immune-allergic rabbit 11 days after termination of cortisone therapy. *B*, soft tubercles in iris stroma in immune-allergic rabbit, seven days after termination of cortisone therapy.

72d day. During this period there was no suggestion of a recurrence of inflammation, or a rebound phenomenon, in either of these two rabbits.

Histological Studies.—A. Eyes of Controls: The histological picture in the untreated immune-allergic control rabbits was similar to that already reported in previous communications—a low-grade, restrained tuberculosis, with discrete, usually encapsulated tubercles and a minimum of inflammatory reaction, caseation, or necrosis.

B. Eyes of Cortisone-Treated Rabbits: The rabbit dying on the 14th day of treatment showed no evidence of any tuberculous lesions in the eyes. Two rabbits dying between the 51st and the 57th day showed several large, fairly discrete tubercles in the iris and ciliary body, some with caseous centers (Fig. 12*A* and *B*). The fourth rabbit, dying on the 57th day, showed the peculiar picture of rows of soft tubercles, with advanced necrosis and caseation and no evidence whatsoever of fibrosis—the picture of advancing caseous tuberculous lesions (Fig. 13*A* and *B*). Bacterial stains of the eyes of these three rabbits revealed many bacilli throughout the lesions. In one animal there were myriad organisms in the caseous centers of the tubercles. In the remaining two rabbits the organisms were both in and around the lesions, many being phagocytosed.

The eye of the rabbit dying on the 67th day of treatment, with a well-marked rebound phenomenon, showed marked edema of the iris and ciliary body and rows

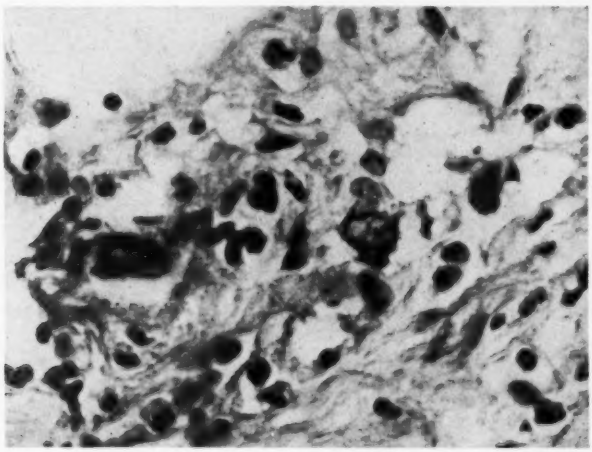

Fig. 15.—Large, basophilic cells in iris stroma of corticotropin-treated rabbit.

of fresh, small tubercles on the iris surface (Fig. 14*A*), together with larger, soft tubercles in the iris and ciliary body (Fig. 14*B*). The edema and fresh, small tubercles apparently were the histologic expression of the violent exacerbation noted clinically. Bacterial stains of this eye showed many bacilli, both in and around the tubercles, widely disseminated throughout the section. The eye of the last rabbit, showing the rebound phenomenon, was not suitable for histological study (post-mortem changes).

C. Eyes of Corticotropin-Treated Rabbits: The rabbits treated with corticotropin showed a somewhat different picture. One rabbit, dying on the 10th day, showed a practically clear eye. The animals dying between the 36th and the 44th day showed occasional small, discrete tubercles, without necrosis, in the stroma of the iris and slight tuberculous infiltration of the ciliary body and the root of the iris. The animal surviving a full 72 days, 12 days after treatment was terminated, showed a number of small, fairly discrete tubercles in the iris, iris root, and ciliary

body. This animal and another dying between the 36th and the 44th day showed a number of peculiar phagocytic cells filled with foamy basophilic reticulum (Fig. 15). The nature of these cells is not immediately evident.

Complete autopsies were not performed on the animals in this experiment, and therefore no report on systemic pathologic changes can be made.

EXPERIMENT 4.—*Technique.*—On Oct. 11, 1950, a series of normal rabbits of either sex and of the same breed as that used in former experiments were inoculated in the groin with 0.5 cc. of a 1:10 dilution of a three-week-old culture of virulent human tubercle bacilli. On March 10, 1951, there were 36 survivors, all in excellent condition. These animals were then tested for cutaneous reactivity to purified protein derivative of tuberculin U. S. P., and all gave positive reactions. They were then divided into five groups of equal cutaneous reactivities and were handled as follows: Group 1 (nine rabbits) was left untreated as a control; Group 2 (nine rabbits) was treated with cortisone, 5 mg. a day in one injection; Group 3 (five rabbits) was treated with corticotropin, 5 mg. a day, in two divided doses; Group 4 (nine rabbits) was treated with Compound F, 5 mg. a day, in one dose, and Group 5 (four rabbits), had both eyes treated topically with cortisone ointment, 25 mg. per gram of base, twice daily.

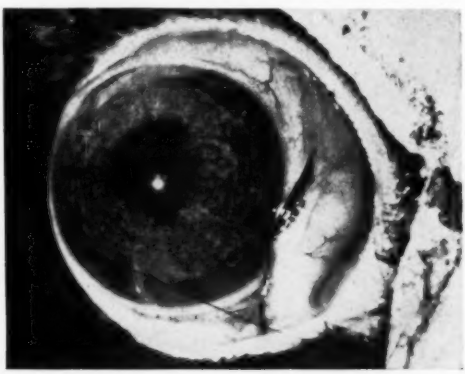

Fig. 16.—Immune-allergic, untreated control, 90 days after inoculation.

Treatment in Groups 2, 3, 4, and 5 was commenced on March 26, 1951, and was continued through May 21, a period of 57 days. The right eyes of all animals in Groups 1, 2, 3, and 4 and both eyes of the rabbits in Group 5 were given injections in the anterior chambers of 0.1 cc. of a suspension of living tubercle bacilli (the same strain used when they received systemic injections) on April 3, 1951. All rabbits were thereafter examined clinically at one to seven day intervals for the period of treatment, and all survivors, for a minimum period of five weeks after treatment was terminated. The intensity of the ocular disease was evaluated on a numerical scale, as in former experiments, and graphs showing the course of the disease in the treated animals and in the controls were prepared.

Clinical Results.—A. Controls: Twenty-four hours after the injection of the tubercle bacilli into the anterior chamber, the eyes given injections showed a sharp inflammatory reaction characterized by pericorneal inflammation, injection of the iris, a contracted pupil, and occasionally a little fibrin in the anterior chamber—the typical picture of nongranulomatous iritis, the focal reaction to the tuberculin in the inoculum. This gradually subsided, and on the 10th day after inoculation a few eyes only showed inflammation, and that a trace. Thereafter there developed a mild and restrained ocular tuberculosis, characterized by a low-grade inflam-

mation of the iris and scattered small, discrete tubercles over the iris and occasionally in the cornea. This continued for approximately seven weeks, then gradually subsided, and on the 82d day after inoculation practically all eyes were quiet, with only a few posterior synechiae and small areas of iris atrophy remaining as residua (Fig. 16). When the last two controls were killed, 198 days after inoculation, the activity in the eyes was rated as 0 on clinical examination.

B. Rabbits Treated Parenterally with Cortisone: The graph in Figure 17*A* shows the comparative course of the clinical disease in the controls (Group 1) and the cortisone-treated rabbits (Group 2). Eight days' treatment with cortisone prior to injection of the tubercle bacilli into the anterior chamber completely blocked the focal reaction to the tuberculin in the inoculum shown by the controls. Thereafter the eyes of the treated animals remained quiet and free of all evidences of inflammation for a period of approximately 32 days, during which time the controls all exhibited a low-grade, but definite, ocular tuberculosis. Beginning about the 32d day after inoculation, or the 40th day of treatment, the eyes of the treated animals began to exhibit tuberculous disease identical with that shown by the controls. The first cortisone-treated rabbit died on the 48th day, and the last on the 55th day, of treatment. During the last week the severity of the clinical ocular picture steadily increased, and at the death of the last of these rabbits of Group 2 there was no difference between the eyes of the controls and the eyes of the treated animals.

C. Corticotropin-Treated Rabbits: The graph in Figure 17*B* shows the comparative courses and clinical pictures of the disease in the controls and the corticotropin-treated rabbits. Eight days' prior treatment with corticotropin effectively controlled the focal reaction to the tuberculin in the inoculum shown by the controls. Thereafter the eyes showed only a minimum of inflammation up to the 48th day of treatment. After this, two rabbits of this group exhibited a low-grade, restrained tuberculosis of a maximum intensity of 0.5 and 1.0, while the other two survivors remained practically free of any evidence of inflammation or ocular tuberculosis during the entire period of treatment. When treatment was terminated, on the 57th day, the average activity for this group was only 0.3. At this time one rabbit was killed for histological study, and the remaining three were kept under observation for a further period of three months. During this period of observation the three surviving rabbits showed no recurrence of inflammation or any clinical evidence of new tuberculous lesions. When the animals were finally killed, 100 days after termination of treatment, the activity in the eyes of all three was rated as 0 on clinical examination.

D. Compound-F-Treated Rabbits: The graph in Figure 17*C* shows the comparative courses of the clinical disease in the controls and the Compound-F-treated rabbits. Eight days' prior treatment with Compound F partially blocked the focal reaction to the tuberculin in the inoculum. Thereafter the eyes of the treated animals exhibited a restrained ocular tuberculosis quite similar to, but at first of somewhat less intensity than, that shown by the controls. When treatment was terminated, on the 57th day, the picture in the surviving treated rabbits was of slightly greater intensity than that in the untreated controls. Immediately after termination of treatment the eyes of the four surviving rabbits of Group 3 showed a sharp increase in the inflammatory reaction with formation of fresh tubercles on the iris and in the cornea, the typical rebound phenomenon shown by the surviving

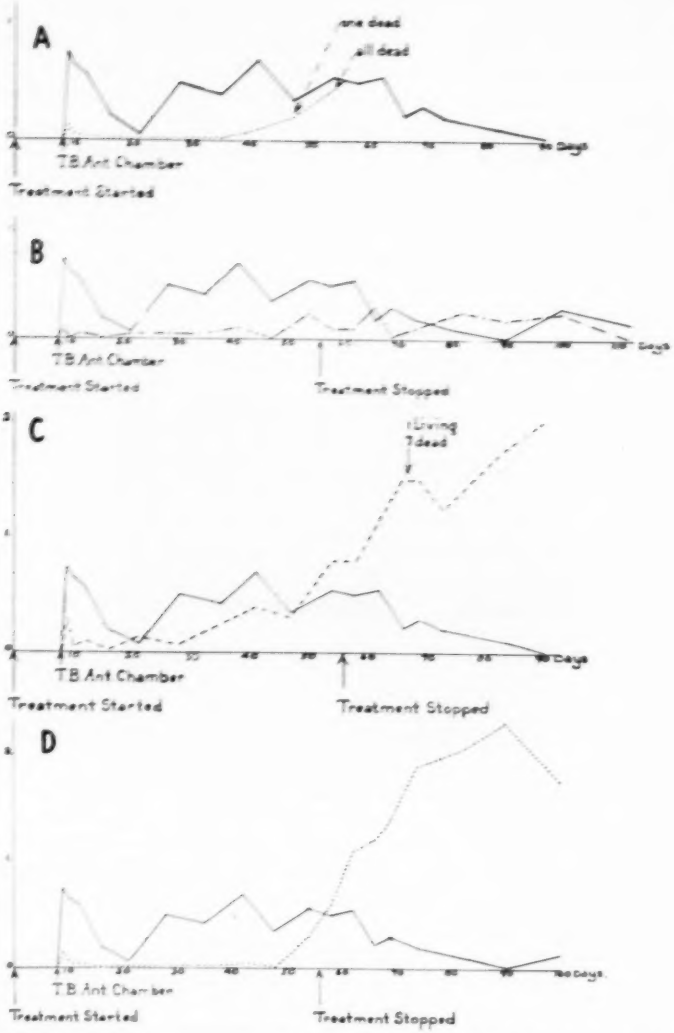

Fig. 17.—*A*, effect of parenterally administered cortisone (dotted line) on development of tuberculous lesions in eyes of immune-allergic rabbits (Experiment 4). *B*, effect of parenterally administered corticotropin (line of dots and dashes) on development of tuberculous lesions in eyes of immune-allergic rabbits (Experiment 4). *C*, effect of parenterally administered Compound F (broken line) on development of tuberculous lesions in eyes of immune-allergic rabbits. *D*, effect of topically administered cortisone ointment (dotted line) on development of tuberculous lesions in eyes of immune-allergic rabbits (Experiment 4). In all graphs the values for control eyes are shown by solid lines.

cortisone-treated rabbits in Experiment 3. Within the next 10 days two of the surviving rabbits died, and the last two survivors were killed on the 90th day after treatment had begun. At that time the disease was active in both eyes; one rabbit had masses of fresh, soft tubercles over the iris, with an estimated activity of 3.

E. Rabbits Treated Topically with Cortisone: The graph illustrating the course of the ocular tuberculosis in the controls and in the rabbits treated by topical application of cortisone is shown in Figure 17*D*. The topical use of cortisone ointment effectively inhibited the focal reaction to the tuberculin in the inoculum shown by the controls and completely inhibited the outbreak of any ocular inflammation or evidence of ocular tuberculosis for a period of 40 days. Thereafter, beginning at the 48th day of treatment and continuing up to the 57th day, when treatment was stopped, a restrained tuberculosis developed in all eyes. At this time the picture in the treated eyes was exactly the same as that in the controls. Immediately after termination of treatment all eyes exhibited a sharp inflammatory reaction, with new tubercles forming in the iris and cornea. At this time one rabbit was killed for

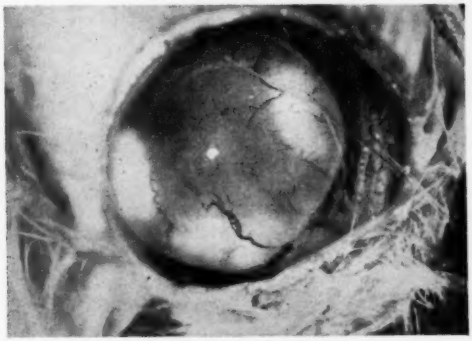

Fig. 18.—External appearance of eye of immune-allergic rabbit treated topically with cortisone, 30 days after termination of treatment, illustrating rebound phenomenon (Experiment 4).

histological study. Within the next five weeks, when two rabbits were killed for histological study, the surviving rabbits all exhibited a picture of violent ocular tuberculosis (Fig. 18), much severer than that shown by any of the controls. The last rabbit, killed after a further period of nine weeks' observation, showed huge caseous tubercles of the cornea. Thus, the rebound phenomenon, after discontinuation of the topical use of cortisone, was acute and violent and quite comparable to the similar phenomenon shown by the cortisone-treated rabbits in Experiment 3 and by the Compound-F-treated rabbits in this experiment.

F. Mortality: Control group: There were no deaths in the control group. Two rabbits were killed for histological study after termination of treatment of the other group, and the rest, at the end of the final period of observation.

Cortisone-treated group: One rabbit died on the 6th day of treatment; one, on the 13th day, and the remaining seven, between the 53d and the 56th day—a mortality of 100% under a 56-day period of treatment.

Corticotropin-treated group: One rabbit died on the seventh day of treatment. Thereafter there were no spontaneous deaths in this group.

Compound-F-treated group: One rabbit died on the 14th day of treatment; one, on the 19th day; one, on the 36th day, and four others, from the 57th to the 67th day. The eighth rabbit died on the 88th day, and the one survivor was killed 2 days later, on the 90th day, 33 days after the 5-week period of post-treatment observation. Thus, there was a mortality of 33% during the treatment and a further mortality of 55% after termination of treatment.

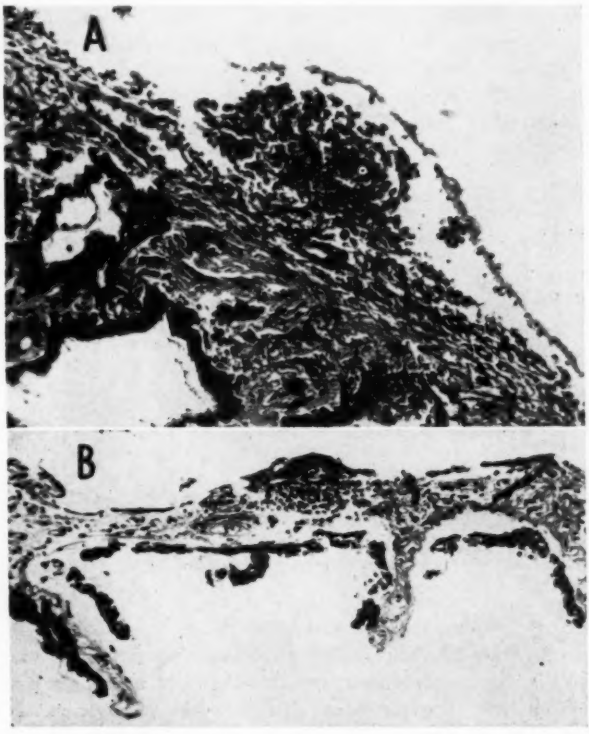

Fig. 19.—*A*, discrete tubercle of the iris in untreated control immune-allergic rabbit, 90 days after inoculation (Experiment 4). *B*, old granulomatous lesion in ciliary process of untreated immune-allergic rabbit, 90 days after inoculation of eye.

Rabbits treated topically with cortisone: One rabbit died on the 61st day, four days after treatment had been terminated, of an incidental cage infection. The remaining three rabbits were killed for histological study at the end of the experiment or after the five-week period of observation.

G. Weight Variation: There was no loss of weight in the controls, the corticotropin-treated rabbits, or the rabbits receiving topical applications of cortisone. The average loss of weight was 0.5 kg. in the rabbits treated parenterally with cortisone and 0.7 kg. in the rabbits treated with Compound F.

Histological Studies.—A. Eyes of Controls: The controls killed at the completion of treatment of the other groups showed minimal lesions, consisting of occasional small, discrete granulomatous lesions in the ciliary body, at the angle, or on the surface of the iris (Fig. 19*A*). The controls killed later showed even less, the old tubercles present being well encapsulated (Fig. 19*B*) or the eyes showing nothing except scarring and a few epithelioid and giant cells.

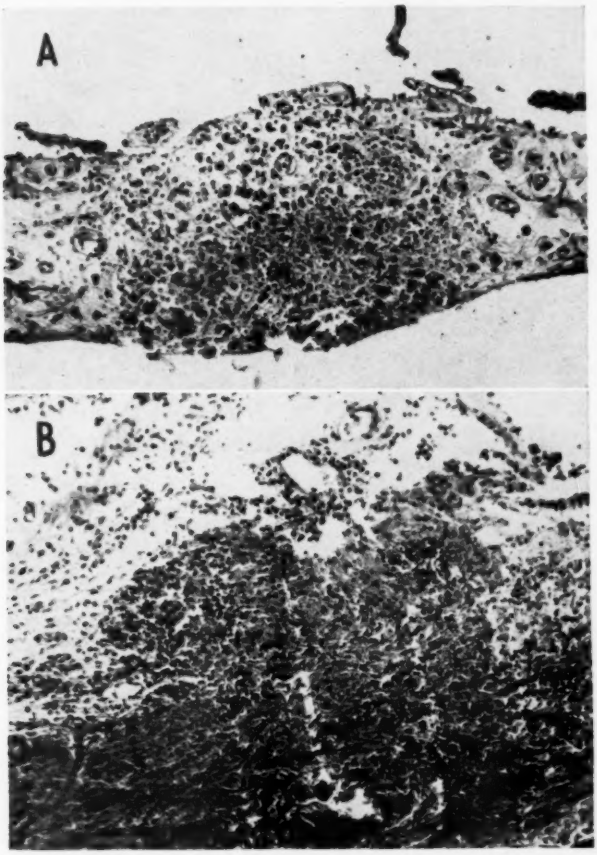

Fig. 20.—*A*, tubercle of iris in immune-allergic rabbit, after 56 days of parenteral treatment with cortisone (Experiment 4). *B*, tubercles of ciliary body in immune-allergic rabbit treated with corticotropin, 36 days after cessation of treatment and 90 days after inoculation (Experiment 4). (× 120.)

B. Eyes of Cortisone-Treated Rabbits: The rabbits treated with cortisone all died within a few days, just at the completion of treatment. The eyes of these animals were quite similar to those of the controls, showing only occasional scattered tubercles with a minimum of inflammatory reaction. The tubercles on the iris,

however, appeared somewhat larger and fresher than those shown by the controls (Fig. 20*A*).

C. Eyes of Corticotropin-Treated Rabbits: The corticotropin-treated rabbit dying on the seventh day of treatment showed no lesions of tuberculosis. The rabbit

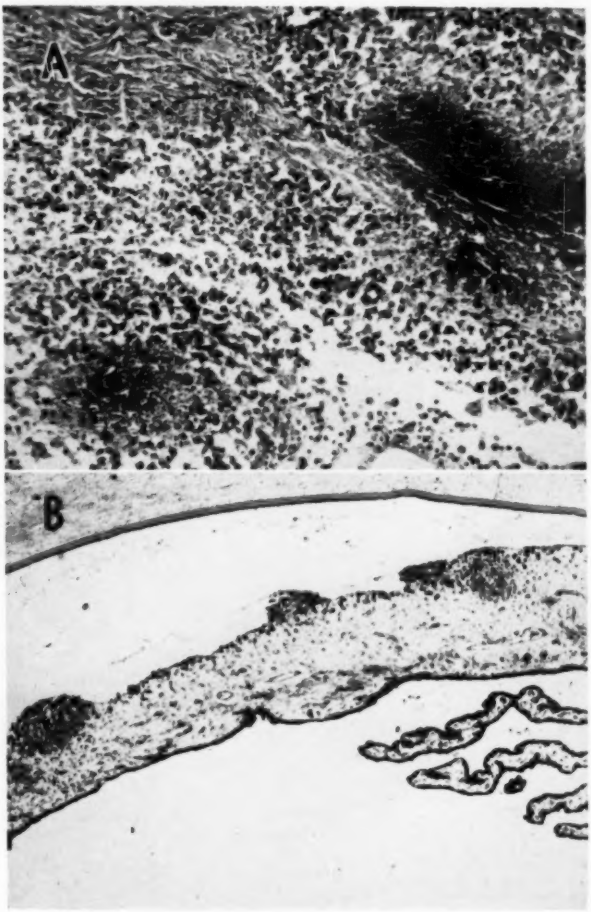

Fig. 21.—*A*, tubercles of angle and ciliary body in immune-allergic rabbit treated with Compound F, 11 days after termination of treatment and 67th day after inoculation (Experiment 4). *B*, fresh tubercles on surface of iris in immune-allergic rabbit treated topically with cortisone ointment, four days after cessation of treatment and 60 days after inoculation (Experiment 4).

killed on the 90th day, 5 weeks after termination of treatment, showed epithelioid-cell tubercles at the angle, not well circumscribed and with a little caseation (Fig. 20*B*).

D. Eyes of Compound-F-Treated Rabbits: The two Compound-F-treated rabbits dying before the 36th day of treatment showed no evidence of ocular tuberculosis. The three animals dying between the 36th and the 59th day showed only minimal tuberculosis with occasional small tubercles, quite similar to the picture in the controls. The remaining four animals died or were killed after termination of treatment. All showed some exacerbation of the clinical inflammation, varying from slight to violent. The sections of the eyes of all these animals showed fresh lesions. In one animal there were large, spreading tubercles of the angle, one with a caseous center, without any evidence of encapsulation or fibrosis (Fig. 21*A*). The eyes of two other rabbits showed fresh, soft tubercles over the surfaces of the iris, quite similar to those depicted in Figure 20*A*. The eye of the last rabbit, which showed the most violent external exacerbation, was, unfortunately, lost in the laboratory and is therefore not available for study.

E. Eyes of Rabbits Treated Topically with Cortisone: The rabbit killed four days after termination of treatment showed clinically a marked increase in the inflammatory reaction and the formation of small, fresh tubercles on the surface of the iris. These tubercles first appeared two days after treatment was stopped. Histological examination revealed fresh tubercles throughout the ciliary body and rows of fresh, soft tubercles on the surface of the iris (Fig. 21*B*). The two animals killed five weeks later both showed advanced tuberculosis, and sections of the eyes revealed large caseous tubercles throughout the ciliary region, iris, and cornea (Fig. 22*A* and *B*). The last animal, killed nine weeks later, likewise showed huge caseous tubercles of the cornea. These lesions were suggestive of the advanced changes uniformly found in the eyes of the nonimmune animals and were entirely different in size and character from the usual small circumscribed lesions shown by the immune-allergic rabbits. There was, however, no invasion of the choroid or the posterior ocular segment.

F. Tissues of the Control Rabbits: No significant gross pathologic changes were found at autopsy in any of the untreated control rabbits. In three of the controls, no lesions of tuberculosis were observed in any tissue on histological examination. The remaining controls showed an occasional tubercle in the lung, liver, spleen, or adrenal gland, usually in one organ only. These tubercles were always well circumscribed and usually well encapsulated. No extensive tuberculous changes were anywhere observed. This is the usual picture before seen in the untreated immune-allergic rabbit.

G. Tissues of Rabbits Treated Parenterally with Cortisone: All nine rabbits treated by parenteral injection of cortisone died while under treatment, the last animal dying on the day treatment was terminated. An interesting gross pathologic change was shown by three rabbits dying on the 54th, 55th, and 56th days of treatment. The fascia over the abdominal muscles was studded with small, whitish droplets of coagulated cortisone, which at first glance resembled miliary tubercles, but which were sterile on culture. Evidently, after the subcutaneous injections, the cortisone had been taken up by the lymphatics and coagulated in small nodules. Except for these, and, in one animal, a large caseous nodule in the groin at the site of the original systemic injection of tubercle bacilli, the autopsies showed no gross pathologic changes.

Histological examination of the tissues revealed no evidence of tuberculosis in six of the nine rabbits receiving cortisone parenterally. Of the remaining three, two

showed old tubercles in the lung, and the third, a well-encapsulated tubercle in the liver. These lesions were quite similar to the lesions shown by the untreated controls, and were quite evidently old lesions remaining as residua of the first systemic infection. There was no evidence of any fresh lesions in any of the tissues of these animals still under the influence of treatment.

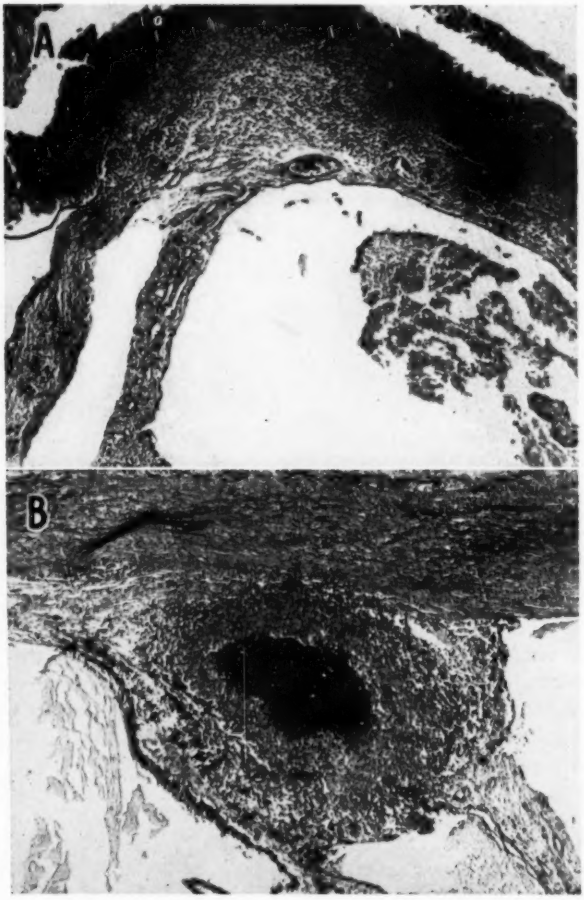

Fig. 22.—*A*, caseous tuberculosis in iris of immune-allergic rabbit treated topically with cortisone ointment, 90 days after inoculation and 34 days after termination of treatment. *B*, caseous tubercle of ciliary body in immune-allergic rabbit treated topically with cortisone ointment, 34 days after termination of treatment and 90 days after inoculation (Experiment 4).

In two animals receiving parenteral injections of cortisone, both dying on the 54th day of treatment, there were occasional small aneurysms in the capillaries of the glomeruli, but without hyalinization. In three of the nine rabbits the adrenals showed some loss of lipid

H. Tissues of Corticotropin-Treated Rabbits: There were no gross changes found at autopsy in any of the corticotropin-treated rabbits. Four of the five rabbits showed histological evidence of systemic tuberculosis. In one rabbit there were numerous circumscribed and encapsulated tubercles in the kidney. In another, small tubercles and giant cells were observed in the spleen. In two others, killed 100 days after cessation of treatment, old tubercles and giant cells were observed in both the liver and the spleen. In one rabbit in this group no lesions were found in the viscera. In general, while lesions of systemic tuberculosis were more frequent in the corticotropin-treated rabbits than in the controls, they were of the same general character—old encapsulated tubercles without caseation, or old dissolved tubercles with persisting giant cells.

I. Tissues of the Compound-F-Treated Rabbits: The autopsies on three rabbits dying, respectively, on the 14th, 19th, and 36th days of treatment showed essentially no gross pathologic changes. One rabbit, dying on the 58th day, showed nodules of coagulated steroid over the abdominal fascia, quite similar to the picture shown by several of the cortisone-treated rabbits. The rabbits dying or killed at the cessation of treatment and up to the 90th day all showed severe emaciation and loss of body weight. Three of these rabbits, dying spontaneously, showed bloody fluid in the pleural cavities, two having a secondary infection of the upper respiratory tract and the third definite pneumonitis. The last two rabbits, killed 34 days after cessation of treatment, showed pronounced emaciation and occasional miliary tubercles over the organs, but otherwise the autopsies showed grossly nothing significant.

Histological examination of the tissues of the Compound-F-treated rabbits, dying during treatment or killed at the termination of treatment, showed changes quite similar to those observed in the untreated immune-allergic controls. Thus, one animal, dying on the 14th day of treatment, showed no tuberculous lesions anywhere. A second rabbit, dying on the 19th day of treatment, showed an old encapsulated tubercle in the liver only, evidently the result of the preceding systemic infection. Rabbits which died or were killed on the 36th, 58th, 59th, and 63d days similarly showed occasional old encapsulated tubercles in the lungs or liver. In another rabbit, dying on the 58th day, the only evidences of tuberculosis were scars and numerous giant cells in the liver.

On the other hand, two Compound-F-treated rabbits showing the rebound phenomenon in the eyes, one dying on the 67th day and one killed on the 90th day (11 and 34 days, respectively, after cessation of treatment) showed radically different pictures. One rabbit showed numerous nodules of epithelioid cells throughout the lungs and liver, without encapsulation, necrosis, or caseation. These apparently represented fresh, early tubercles. The second rabbit, killed on the 90th day, showed a large, well-encapsulated caseous tubercle, peribronchial lymph nodes, and adjacent tuberculous pneumonitis. In the spleen were numerous small tubercles and nests of epithelioid cells. The histological changes in these two rabbits suggested that there had been a fresh dissemination of bacilli throughout the body, paralleling the exacerbation of tuberculous disease in the eye.

In five of these nine Compound-F-treated rabbits small capillary aneurysms with some hyalinization were present in the glomeruli of the kidney. These were exactly similar to the glomerular changes observed in the normal rabbits treated with Compound F and to the changes occasionally noted in the cortisone-treated rabbits.

J. Tissues of Topical Cortisone-Treated Rabbits: Autopsy on the three immune-allergic rabbits treated by instillation of cortisone ointment in the conjunctival sac failed to show gross pathologic changes. On histological study two rabbits showed several small, well-encapsulated tubercles in the lung. These were well-circumscribed, quite similar to the tubercles found in the untreated controls, and were undoubtedly the residua of the primary systemic infection. The other two rabbits in this group showed no tuberculous lesions in any of the tissues examined.

COMMENT

While the number of animals in each of the experiments is not sufficient to warrant strong conclusions from an individual group, nevertheless, the sum of data from all experiments justifies firm conclusions. The experiments on normal animals (Experiments 1 and 2) clearly show that the inhibitory effect of both cortisone and corticotropin on ocular inflammation fails completely when subjected to the severe test of controlling tuberculous inflammation in the normal animal. During the 46-day period of treatment in Experiment 1, with the large daily dose of 10 mg., these agents had no effect either on the degree of the subjective inflammatory reaction in the eyes or on the objective and histological evidence of organic tuberculous disease. In Experiment 2, in which the periods of observation were 53 and 56 days, and the dose of the hormones and the inoculum of bacilli in the eyes were one-half those given in Experiment 1, an exactly similar result was noted. The conclusion appears inescapable that the ability of these agents to control ocular inflammation is only relative and fails completely when too severe a task is imposed on their capabilities. This bears out the observations previously reported on the action of cortisone and corticotropin on ocular inflammation due to irritants.

The question of an adverse action by cortisone or corticotropin on the course and development of ocular tuberculosis, or on the dissemination of bacilli from the eye to the viscera, is difficult to evaluate in these experiments on normal animals. Histological examinations of the eyes and tissues of the cortisone-treated animals immediately at the termination of treatment revealed no significant increase in the severity of the lesions in the treated animals as compared with that in the controls. However, when other controls and treated animals were killed five weeks later (Experiment 2), there was a significant difference in both the ocular and the systemic lesions of the two groups. The cortisone-treated rabbits showed severer ocular lesions and much more extensive systemic lesions than did the controls. In the corticotropin-treated rabbits the picture was not so clear-cut. Both rabbits killed five weeks after termination of treatment showed a pronounced increase in the ocular tuberculosis, but only one showed extensive systemic lesions. What evidence there is suggests that in the normal, nonimmune rabbit treatment with cortisone or corticotropin results after termination of therapy in a later aggravation of the local lesions and an increased dissemination of bacilli from the site of inoculation throughout the body. There is no evidence indicating what factors may be responsible for this apparent alteration in the pattern of the disease.

Compound F appears to be somewhat in a class by itself. Interest in this compound is especially excited by experimental evidence [8] indicating that when the

8. Hechter, O.: Corticosteroid Release from the Isolated Adrenal Gland, Federation Proc. **8**:70 (March) 1949.

adrenals are perfused with corticotropin, Compound F, and not cortisone (Compound E), is secreted. In this experiment, on normal animals, the parenteral injection of Compound F in doses of 5 mg. a day had a pronounced effect on the carbohydrate metabolism,[9] caused a marked loss of body weight, and produced a mortality of 84% in the treated rabbits. While still undergoing treatment, the eyes of the rabbits treated with Compound F showed more extensive and spreading tuberculosis than did either the untreated controls or the cortisone-treated rabbits. Similarly, the Compound-F-treated rabbits showed much severer systemic tuberculosis than did any of the other groups—untreated controls or cortisone-treated or corticotropin-treated animals. There appears to be no doubt that treatment with Compound F resulted in severer ocular disease and a greater dissemination of bacilli from the eye. Whether this is due to a direct action of the Compound F or whether it is an expression of the general weakness and emaciation of the animals is an unanswered question.

The experiments on immune-allergic rabbits (Experiments 3 and 4) give a much clearer picture of the effect of these agents on the development of ocular tuberculous lesions and confirm the suggestive evidence from the experiments on normal animals. When a much less severe test is imposed on the capabilities of these drugs, it becomes evident that they have an inhibitory action on the early inflammatory phases of tuberculous disease.

Both cortisone and corticotropin, when administered for eight days prior to injection of tubercle bacilli into the anterior chambers, effectively blocked the focal reaction to the tuberculin in the inoculum. Thereafter, for a period of 10 to 30 days, these hormones blocked both the subjective inflammation and the objective evidence of organic disease shown by the untreated controls. It is obvious, however, that they did not affect the propagation of bacilli in the eye, and when the concentration of bacilli became too high they could no longer protect the tissues against the development of lesions; and thereafter during the period of treatment the disease in the eyes of the treated animals ran a course quite similar to that of the untreated controls. There was, however, no evidence of an increased dissemination of bacilli throughout the body tissues in any of the cortisone- or corticotropin-treated animals.

Compound F was much less effective. Eight days' treatment prior to inoculation of the eyes only partially blocked the focal reaction to the tuberculin in the inoculum and thereafter had only a very doubtful effect either on the subjective inflammatory reaction or on the early development of ocular lesions. The Compound-F-treated rabbits showing the rebound phenomenon in the eyes also showed evidences of increased dissemination of bacilli throughout the body.

The most interesting finding in these experiments is what has been termed the rebound phenomenon. This was suggested in the experiments on normal animals, but was clear-cut and definite in Experiments 3 and 4, on the immune-allergic animals. This phenomenon was present in all the survivors in the group receiving cortisone parenterally and in the Compound-F-treated group and reached its highest intensity in the group treated topically with cortisone ointment. It was not observed in any of the animals treated with corticotropin.

Within 24 to 48 hours after the termination of cortisone or Compound-F therapy, the inoculated eyes of the immune-allergic rabbits showed a violent increase

9. Results to be reported in a subsequent communication.

in the degree of inflammation. Fresh tubercles rapidly formed on the surface of the iris and in the periphery of the cornea, which became infiltrated and hazy. These iridic and corneal tubercles increased in size and became caseous. As the rebound phenomenon intensified, the eyes began to undergo buphthalmos, and the clinical and histological pictures began to assume the appearance of the fulminating, necrotizing, and caseating tuberculosis usually seen only in the eyes of the normal, or non-immune, rabbit. The eyes of rabbits killed at the beginning and at the height of the rebound phenomenon were all found swarming with bacilli when the sections were stained for acid-fast organisms.

What is the pathogenesis of this rebound phenomenon? When this investigation was undertaken, it was suggested that adrenocortical hormones might adversely affect the course of ocular tuberculosis by depressing immunity or inhibiting the acquisition thereof, by suppressing the fibroblastic reaction, or by actually damaging the animal's own adrenal cortex to the extent that it was left defenseless when treatment was terminated. Did any of these factors operate in the pathogenesis of this rebound phenomenon?

There is no real evidence that there was any alteration in the immunity. The animals used in Experiments 3 and 4 were highly immune. This is exemplified by the fact that the ocular disease in the untreated controls was of low degree (1.0 in Experiment 3 and less than 1.0 in Experiment 4), while in normal rabbits of the same breed, inoculated at the same time with one-fifth the number of bacilli (Experiments 1 and 2) there developed violent ocular disease (3.0 +) with rupture of the globe in 50% of the inoculated rabbits. Despite the violent character of the ocular rebound phenomenon in the cortisone-treated immune-allergic rabbits, there was no evidence of an increase of tuberculous lesions in the viscera, and it would seem improbable, therefore, that there was any depression of the systemic immunity. There was evidence, it is true, of increased visceral lesions in the Compound-F-treated rabbits showing the rebound phenomenon, but any depression in the systemic immunity which might have existed in this group can readily be attributed to the weakened and emaciated condition of the animals, rather than to any specific action of the administered hormone.

It is quite probable that the suppression of the early inflammatory reaction and of the fibroblastic reaction may be concerned in the rebound phenomenon. There was quite evidently a marked increase in the growth of the bacilli in these eyes, for sections of the eyes enucleated 72 hours after the termination of treatment, in the early stage of the rebound phenomenon, when stained for acid-fast organisms, were found swarming with bacilli. Histological examination of these eyes, and of other eyes enucleated late in the rebound phenomenon, showed a conspicuous absence of any fibrotic reaction. It is quite likely that the great increase in the number of bacilli in the eye, together with the withdrawal of the protective action of cortisone, may be one factor in the pathogenesis of the rebound phenomenon, which is essentially the transformation of the restrained tuberculosis of immune-allergic rabbits into the violent, necrotizing, and caseating type of tuberculosis usually seen only in the normal, nonimmune animal. In this respect, it may be recalled that Rich has shown that such a reversal of the usual picture can be produced by increasing either the number or the virulence of the infecting bacilli, and so overwhelming any immunity which may be present. A second factor is probably the suppression of

the fibroblastic reaction by the cortisone, for, after all, the essence of healing in tuberculosis is bacteriostasis and the encapsulation of the lesion by fibrosis.

The influence of the early suppression of inflammation brings up an interesting question. Friedenwald and his co-workers [10] showed that if the hypersensitivity to tuberculoprotein is abolished by desensitization of immune-allergic guinea pigs with tuberculin the underlying immunity is undisturbed, there is no undue multiplication of the bacilli, and minimal lesions result. Woods and Burky [11], similarly showed that desensitization with tuberculin in immune-allergic rabbits with secondary ocular tuberculosis resulted in suppression of the inflammatory reaction and rapid subsidence of active tuberculous lesions. Thus, we have the paradox that suppression of the inflammatory reaction by tuberculin desensitization does not lead to a multiplication of the bacilli and does promote healing, while suppression of inflammation by cortisone apparently permits a rapid local multiplication of the bacilli and renders the eyes liable to spreading and disastrous tuberculous lesions. The explanation of this paradox is not entirely clear. It is probably due to a difference in the mechanism of suppressing inflammation, which for cortisone is as yet unknown and for tuberculin is the abolition of the hypersensitive state. In the case of cortisone there is an accompanying suppression of the fibroblastic reaction, while in tuberculin desensitization there is no such suppression.

Combined Weights of Adrenals and Relation to Body Weight in Immune-Allergic Rabbits

Treatment	Average Body Weight, Kg.	Average Combined Weight of Adrenals, Mg.	Adrenal Weight per Gram of Body Weight, Mg.
Untreated controls	3.7	537	0.14
Parenteral injection of cortisone	4.45	320	0.07
Corticotropin	3.70	690	0.19
Compound F	2.7	405	0.15
Topical use of cortisone	3.7	520	0.14

Damage to the animal's own adrenal cortex by exogenous cortisone or Compound F, thus leaving the animal defenseless when such exogenous hormone is withdrawn, may be a contributing factor and may account for the absence of the rebound phenomenon in the corticotropin-treated rabbits. In a number of the immune-allergic rabbits the adrenals were stripped of the surrounding fat and adventitious tissue and weighed. The available figures on these weights and their relation to body weights are shown in the accompanying table.

It is immediately apparent that there were a relative atrophy of the adrenals in the rabbits treated parenterally with cortisone and hypertrophy of the adrenals in the rabbits treated with corticotropin. The average weight of the adrenals of the corticotropin-treated rabbits killed at the termination of treatment was 640 mg. The average weight of the adrenals of the rabbits killed three months after termination of treatment with corticotropin and showing no rebound phenomenon in this period had a combined average of 703 mg. These figures indicate that the

10. Rothschild, H.; Friedenwald, J. S., and Bernstein, C.: Relation of Allergy to Immunity in Tuberculosis, Bull. Johns Hopkins Hosp. **54**:232 (April) 1934.

11. Woods, A. C., and Burky, E. L.: Experimental Studies in Ocular Tuberculosis: VII. Effect of Desensitization with Tuberculin in Experimental Ocular Tuberculosis, Arch. Ophth. **29**:369 (March) 1943.

adrenal hypertrophy produced by the corticotropin had been maintained after termination of treatment and the animals were not deprived of the protective action of their own endogenous cortisone. There is no evidence that the apparent adrenal atrophy in the cortisone-treated rabbits contributed to the rebound phenomenon, for the animals treated locally with cortisone showed the most pronounced rebound phenomenon and had no adrenal atrophy.

Turner and associates,[12] in a recent report on the alteration of the lesions of experimental syphilis by treatment of the infected animal with cortisone, has reached a somewhat similar conclusion. He has suggested that the local changes are primarily an alteration of the mucopolysaccharides of the ground substance, which permits accumulation of the hyaluronic acid and suppression of chondroitin sulfate. Leyton's recent experiments with radioactive sulfur in cortisone-treated animals lend color to this theory.

Is there an alteration of the mucopolysaccharides or an accumulation of hyaluronic acid in the tuberculous eyes of rabbits treated with cortisone, Compound F, or corticotropin? A full answer to this question would require biochemical measurements, which were not included in the experiments here reported. Histological examination of the eyes of immune-allergic rabbits which died during the course of treatment or after termination of treatment showed a slighter tendency to fibrosis and encapsulation of the tubercles in the treated animals than in the untreated controls. Since, presumably, the fibrous tissue contains the sulfated mucoids, it is probable that there was less of this material in the infected ocular tissues of the treated animals than in the controls.

Histological examination of the eyes, however, does not answer the question why there is diminished fibrosis. This decrease may be the result of the early suppression of the inflammatory reaction. On the other hand, treatment with the adrenocortical hormones may render the animal less capable of manufacturing the sulfated mucoids. No basophilia of the ground substance surrounding the lesions was noted. Such basophilia might be expected if there were a local accumulation of hyaluronic acid.

Whatever ultimately may prove to be the explanation of the rebound phenomenon, these experimental studies indicate clearly the potential dangers of the use of cortisone, either parenterally or locally, in ocular tuberculosis. They likewise offer an explanation for two clinical near-disasters recently observed in the Wilmer Institute. Two patients who had each previously lost one eye from ocular tuberculosis were admitted to the wards with active tuberculous choroiditis in the second eye. There appeared to be no doubt whatsoever of the etiological diagnosis. The condition of both patients was critical. They were treated in an identical manner. They were given a full course of systemic injections of cortisone over a 10-day period, and the dose was then gradually tapered off, the idea being to control the immediate exudative reaction of the disease. At the same time, treatment with streptomycin was started, with thiazolsulfone (promizole®) or paraaminosalicylic acid as the adjuvant. Both patients showed an immediate favorable response. The choroidal exudates became circumscribed, and as the streptomycin and adjuvant

12. Turner, T. B.; Hollander, D. H., and Rice, F. A. H.: Cortisone in Experimental Syphilis, presented at the Fourth Annual Symposium of the American Venereal Disease Association, Washington, D. C., April, 1951.

therapy caught hold, on the 12th to the 16th day, the eyes began to clear. After 7 to 10 weeks of therapy the patients were discharged with clinically quiet eyes and excellent vision. All appeared well. Within one week one patient returned with a violent exacerbation of the choroiditis, and within six weeks the second patient returned with a similar recurrence. These recurrent lesions were of greater intensity and extent than the original ones. Fortunately, with renewed and prolonged streptomycin and adjuvant therapy, the disease in both patients was again brought under control, with the preservation of good vision. The analogy between the clinical picture in these two patients and the experimental findings is striking and clearly indicates that the use of cortisone and corticotropin is contraindicated in ocular tuberculosis. These hormones radically alter the entire natural pattern of the disease, and the indications are that this alteration is not for the ultimate good either of the patient or of the experimental animal.

When corticotropin and cortisone were first used in the treatment of clinical disease, it was fully realized that they were powerful and potentially dangerous hormones. On account of their general physiologic action, they were believed to be contraindicated in such metabolic diseases as diabetes and hypertension. The dangers of their prolonged use, the possibility of the production of Cushing's syndrome (pituitary basophilia) or of permanent adrenal damage, were fully realized. There were also warnings that their action on infections was undetermined, and there was theoretical reason to believe that they might be contraindicated in tuberculosis. As knowledge of their action has gradually extended, it is becoming evident they can alter for the worse the pathogenesis of some chronic infectious diseases—certainly syphilis and tuberculosis. Their limited range of usefulness in ophthalmic therapeutics is gradually becoming defined. It is probable that we have much more to learn of other contraindications.

SUMMARY AND CONCLUSIONS

1. When subjected to the severe test of ocular tuberculosis in the normal, nonimmune rabbit, cortisone, corticotropin (ACTH) and Compound F have no effect in controlling either the subjective inflammatory symptoms or the development of organic tuberculous lesions.

2. After treatment with these agents is terminated in the normal animal, there are slight accentuation of the local ocular inflammation and some inconclusive evidence of a further systemic dissemination of the organisms.

3. When subjected to the less severe test of ocular tuberculosis in the immune-allergic rabbit, cortisone, given either parenterally or topically, and corticotropin, given parenterally, will block the focal reaction to tuberculin in the inoculum which occurs when tubercle bacilli are injected into the anterior chamber and will block the early development of tuberculous lesions.

4. After a period of from 30 to 45 days, the bacilli multiply in the eyes to the extent that these agents are no longer capable of blocking either subjective inflammation or the development of organic lesions.

5. In these experiments Compound F appeared to be less effective than either cortisone or corticotropin in suppressing the focal reaction to tuberculin in the inoculum, the early inflammatory reaction, and the development of tuberculous lesions.

6. After treatment with cortisone or Compound F is terminated in immune-allergic rabbits there is a violent increase in the degree of ocular inflammation, with the development of acute and spreading tuberculous lesions in the eye—the rebound phenomenon. The possible pathogenesis of this rebound phenomenon is discussed.

7. The evidence at hand indicates that the rebound phenomenon is probably due chiefly to a local change in the eye which permits the multiplication of the bacilli to the point that all immunity is overwhelmed, and thereafter the tuberculous disease assumes the destructive, necrotizing, and caseating character of tuberculosis in the nonimmune animal. Depression of the animal's own adrenal cortex and inhibition of fibrosis may be additional factors.

8. Animal experimentation and clinical observation both indicate that certainly cortisone and Compound F, and probably corticotropin, are contraindicated in ocular tuberculosis.

Wilmer Ophthalmological Institute.

Clinical Notes

AN IMPROVED MANUALLY OPERATED ERYSIPHAKE

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THE GRASPING of the lens capsule by suction for cataract extraction has appeared to many surgeons to be the ideal method. Whether this method is superior to the use of a satisfactory capsule forceps is a question which will not be answered for many years, until the manually operated erysiphake shall have been tried by many surgeons with all types of cataracts. Dimitry,[1] Bell,[2] and Harrington [3] have pointed out the advantages of the simplified erysiphake over the mechanical vacuum-pump erysiphake. Harrington [3] has described a simplified instrument and has also indicated the need for further improvement and simplification.

Manually operated suction devices appear to have two chief weaknesses: awkwardness of manipulation and a very limited degree of vacuum. It has been demonstrated that the high degree of suction produced in pump-operated devices is not necessary, and may even be hazardous. On the other hand, the manually operated devices available to date have not produced enough suction to make the surgeon feel confident that he could manipulate the instrument without pulling it off the lens. It occurred to me that a possible correction of both the defects mentioned lay in the adoption of the mechanism used in certain fountain pens. The filling principle of these pens is the compression of a rubber or plastic sac against the lumen of a rigid tube. The volume of fluid displaced in this manner is much greater than that which can be displaced by compressing the same sac between the thumb and finger. Consequently, a higher degree of suction may be obtained given the same elastic sac. The metal tube in which the sac is contained is made of thin stainless steel or aluminum and has a section cut away to permit compression of the sac. It was found that this mechanism was so light in weight that it was little heavier than the ordinary contact-lens sucker. A Bell or Dimitry type of cup was inserted into this fountain-pen mechanism and was found to work extremely well as an erysiphake. This served as the pilot model for the instrument to be described.

The instrument is extremely simple, consisting of a thin aluminum tube, containing a short piece of rubber tubing closed at one end. The metal housing is 7 cm. long and 8 mm. in diameter. On one side of it a window, 8 by 40 mm., is cut out to permit compression of the rubber tube against the lumen of the metal tube by two of the operator's fingers. The rubber tubing is a 3.5-cm. length of ordinary 5/16-in. intravenous tubing. A rubber plug is provided at one end. The erysiphake tip is simply pushed into the open end of the rubber tube. This expands the tubing enough so that when it is drawn into the metal housing it fits very snugly. An improved suction cup, which is tapered toward the leading edge for ease of entrance through the corneal section, is now provided by the manufacturer.[4]

The instrument may be sterilized by boiling or autoclaving or with antiseptic solutions. It may be used filled either with air or with sterile saline solution. The tube is usually com-

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1. Dimitry, T. J.: Evolution of a Suckling Disc for Intracapsular Extraction of Cataract, Arch. Ophth. **21**:261 (Feb.) 1939.

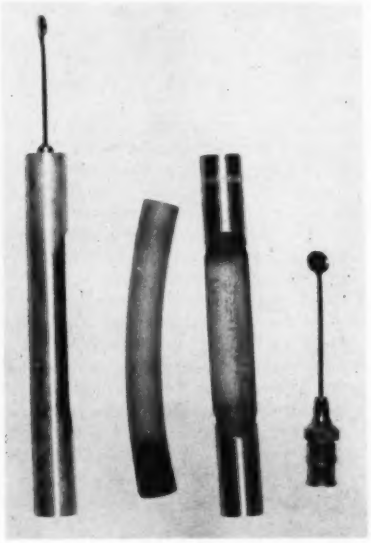
2. Bell, A. E.: A Modified Erisophake, Am. J. Ophth. **31**:610 (May) 1948.

3. Harrington, D. O.: A New and Simplified Erisophake, Am. J. Ophth. **34**:435 (March) 1951.

4. Parsons Optical Laboratories, San Francisco.

pressed and emptied before the instrument is inserted into the anterior chamber. However, if blood or uveal pigment is present in the anterior chamber, it may be washed out of the eye by filling the erysiphake with sterile saline solution and compressing the tube after the tip is in the anterior chamber. It will be found that a fine, gentle stream results, which is admirably suited to the purpose. The cup is then applied against the anterior surface of the lens in the usual manner, and the rubber tube is released.

The suction cup may be rotated to face in any desired direction in relation to the opening in the tube. In my experience, it has seemed advantageous to face the concavity of the suction cup in the same direction as the opening in the tube. In this way the pressure of the fingers when compressing the rubber is in a direction away from the interior of the eye. Thus, the hazard of inadvertently pushing too firmly on the lens and dislocating it backward is minimized.



Erysiphake assembled (left) and component parts: rubber tubing; aluminum handle; suction disc.

The volume of fluid which the instrument displaces with a single compression of the rubber tube is approximately 0.5 cc. The negative pressure produced is such that the entire instrument may be suspended from the skin. In enucleated eyes with sufficiently strong zonules the entire globe could be lifted by the erysiphake. The weight of the instrument, including the cup, is only 5.7 gm. This lightness makes it possible, if necessary, to change the position of the hand or fingers while the erysiphake is attached to the lens. The greater suction makes it feasible to tumble the lens, as in a forceps extraction.

Although the instrument described here is similar in appearance to the one described by Harrington, it differs in one important detail. The metal tube not only serves as a rigid handle for more delicate control but is an integral part of the sucking mechanism, providing a higher degree of vacuum.

The instrument has been found particularly valuable in the removal of intumescent, hypermature, and subluxated cataracts. The results with all types of cataracts have been so satisfactory that it has, for me, replaced the capsule forceps almost completely.

Fig. 1.—Teaspoon penetrating the eye orbit.

Fig. 2.—Appearance of the eye 10 days later.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistent with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

TEASPOON PENETRATING CHILD'S ORBIT

Orbital accidents to children are an everyday occurrence. We have all seen youngsters who have had the misfortune to injure the eye with a knife, fork, dart, scissors, or like sharp implement.

Recently, on Sept. 26, 1951, I saw a baby 19 months old who had been brought to the Children's Hospital in Buffalo from a nearby town with the handle of a common teaspoon penetrating the right orbit a distance of 5.6 cm. (2½ in.) from the inner lower orbital rim. The child had fallen from the top of a high chair, upon which she was standing, to the floor while holding the spoon tightly in her right hand. It penetrated the inner lower right eyelid, forced the globe upward and lateralward, and continued in along the nasal wall.

Examination was carried out with the child under general anesthesia. The fundus appeared normal; the disk was of good color and evenly defined. Very slight nasal bleeding was noted by a rhinologist, who thought it came from the ethmoid area. The spoon, tightly wedged in, was carefully withdrawn to avoid any further damage or hemorrhage. The skin was cleansed; the orbital tissue replaced, and the lid wound closed with five fine silk sutures. Atropine ointment and aureomycin ointment were applied, with the eye closed by an ordinary pad.

A preparation of crystalline procaine penicillin G in oil (duracillin®), 400,000 units, was prescribed and the child was admitted to the hospital for observation and consultation.

Neurologic, rhinologic, and roentgenologic studies revealed no abnormality, the neurologist giving the opinion that the blunt end of the spoon had lost its force, denting, but not penetrating the dura.

The fundus remained normal, as did the optic disk. The child was hospitalized 10 days, during which the temperature was not elevated. Use of the penicillin was discontinued after five days.

At discharge there appeared to be no interference with the normal ocular movements, no intraocular complications, and no interference with the lacrimal drainage.

I might be criticized for not having roentgenograms taken with the spoon in position, but this was not done because the child was in severe pain and had undergone a journey of almost 30 miles to the hospital, and the admission was during the late evening hours.

The kodachrome® with the spoon in position had been taken by the resident before my arrival.

This case is reported to emphasize the importance of antibiotics in the management of such injuries and the rarity of the injury, no such accident having been noted by any local ophthalmologist or known to have occurred in the experience of any one spoken to at the (1951) Academy meeting.

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Annual Reviews

LENS AND VITREOUS

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DURING the past year a number of important contributions to the literature of the lens and vitreous have appeared. Several reports have dealt with lens surgery in the young. The electron microscope has been applied to the study of the vitreous. A renewed interest in irradiation cataract is evident, and the irradiation factors in the experimentally induced x-ray and microwave cataract are now well defined. Although considerable advance has been made in knowledge of the chemical and enzymatic processes involved in lens metabolism, there has been as yet no conclusive substantiation of any of the many theories of cataract formation. It is clear that certain chemical and metabolic changes accompany structural deterioration of the lens substance, but it has not been possible for the most part to demonstrate that these changes precede the development of cataract and may be therefore linked to its causation.

THE LENS

STRUCTURE; CHEMISTRY; METABOLISM

Ultrastructure.—Using the "double-print" technique, Sebruyns [1] studied the ultrastructure of the lens with the electron microscope. He found that the cytoplasm of the cortical cells somewhat resembles that of the renal and hepatic cells; the vacuoles are irregularly arranged and have the classic spongioid appearance. In the nucleus, however, the vacuoles are rectangular and arranged in parallel rows. The author states that it thus appears that the structure of the lens is correlated with its main physiologic properties, i. e., transparency and accommodative power.

Water and Inorganic Ions.—Pau [2] weighed the intact animal lens immersed in a physiologic medium under a variety of conditions. The slower rate of weight increase in younger than in older lenses he considers indicative of a higher degree of integrity of the lens capsule as regards the uptake of water. Injury to the cornea or sclera did not affect the weight of the lens, but the slightest damage to the zonular attachment resulted in a great increase in weight. Death, enucleation, or rupture or disease of the zonules caused a change in the capsular permeability which allowed fluid to enter the lens.

Radioactive tracers were used by von Sallmann and Locke [3] in a study of the effect of x-irradiation on the permeability of the lens and of the blood-aqueous

1. Sebruyns, M.: Ultrastructure of the Cornea and the Lens Studied by Means of the Electron Microscope, Am. J. Ophth. **34**:1437-1442, 1951.

2. Pau, H.: Die Linsenquellung im physiologischen Milieu, von Graefes Arch. Ophth. **151**:352-364, 1951.

3. von Sallmann, L., and Locke, B.: Experimental Studies on Early Lens Changes After Roentgen Irradiation: II. Exchange and Penetration of Radioactive Indicators (Na^{24}, K^{42}, I^{131}, P^{32}) in Normal and Irradiated Lenses of Rabbits, A. M. A. Arch. Ophth. **45**:431-444 (April) 1951.

barrier. In the early, vacuolated stage of x-irradiation cataract, an increased uptake of radiosodium was demonstrated, which was considered to be associated with the increase in extracellular water. Radiopotassium rapidly permeated the normal lens; a diminution in its uptake could not clearly be shown in the cataractous lens with the method used. The author postulates an increased permeability of the cataractous lens with respect to radioiodine, the uptake of which substance was 50 to 100% higher than in the normal lens. Radiophosphorus penetrated the normal lens well, and autographs indicated its higher concentration in the germinating zone near the equator and in the outer cortex. Diminution in the uptake of radiophosphorus could not be demonstrated early in the cataractous process, but could be shown only later, when the stage of total cataract was approached. These experiments did not give weight to the theory that changes in capsular permeability or diminution of phosphorylation processes cause opacification of the lens, but, rather, suggested that these are the accompaniments of the pathologic changes.

Harris and Gehrsitz [4] have investigated the effects of various factors on the sodium, potassium, and water content of the in vitro rabbit lens maintained in Tyrode's solution. These factors included refrigeration; absence of glucose, magnesium, or calcium, and poisonings with sodium cyanide, sodium fluoride, or iodoacetic acid. In all cases there was an increase in the sodium and water contents of the lens. Whether the derangement of the normal sodium-potassium ratio resulted from a lowering of metabolic activity, which interfered with an active transfer mechanism for sodium, or from an increased capsular permeability for sodium was not elucidated. It is the authors' opinion that this cation shift, rather than being secondary to the development of intumescence, is important in its causation.

Ascorbic Acid and Enzymes.—François and Rabaey [5] detected the presence of ascorbic acid between the lens fibers, using a method in which this substance reduces silver nitrate. They found little difference between the amount in the cortex and in the nucleus.

According to François and Rabaey [6] the lens contains little or no alkaline phosphatase. They found the enzyme to be present only in the epithelial cells, where it was concentrated mainly at the equator. Corrado [7] succeeded in demonstrating the presence of an enzyme of the nicotinic-acid group (vitamin P-P) in the lens of the ox. De Vincentiis and Auricchio [8] found amino-acid oxidase in the lens, indicating that the lens is capable of deaminating amino acids. The lowering of the glucose metabolism in animal lenses made cataractous by massage was demonstrated by Bonavolontà.[9] He found the glucose content of the aqueous in these

4. Harris, J., and Gehrsitz, L.: Significance of Changes in Potassium and Sodium Content of the Lens, Am. J. Ophth. **34**:131-138 (May, Pt. 2) 1951.

5. François, J., and Rabaey, M.: Localization histo-chimique de l'acide ascorbique réduit dans l'œil de certains mammifères, Ann. ocul. **183**:829-850, 1950.

6. François, J., and Rabaey, M.: Localisation histochimique de la phosphatase alcaline dans l'œil de certains mammifères, Ann. ocul. **184**:481-497, 1951.

7. Corrado, M.: Sui derivati della vitamina PP nell'acqueo e cristallino con particolare riguardo al D. P. N., Gior. ital. oftal. **3**:248-263, 1950; abstracted, Am. J. Ophth. **34**:317, 1951.

8. de Vincentiis, M., and Auricchio, G.: Sur le metabolisme des acides aminés dans les tissus oculaires, Acta ophth. **28**:7-22, 1950.

9. Bonavolontà, G.: Sui rapporti fra composizione dell'umore acqueo e metabolismo del cristallino, Ann. ottal. e clin. ocul. **76**:247-265, 1950.

animals to be abnormally high, whereas the lactic-acid content was low. In a study of the glycolytic activity of the in vitro lens, Ferrante [10] measured the amounts of lactic acid produced with and without the phosphorylating enzyme system. He concludes that the glycolytic cycle is largely dependent on the phosphorylation mechanism, but that another mechanism also exists. Ely [11] demonstrated that the aerobic phase of glucose metabolism may involve the functioning of the citric-acid cycle in the oxidation of pyruvate. Bovine-lens homogenates were shown to display dehydrogenase activity capable of oxidizing a number of substances in the citric-acid cycle. It was found that the addition of cytochrome C was necessary in order for maximal oxidation of α-ketoglutarate to take place. Daily, Zeller, and co-workers [12] report the existence of an adenosinetriphosphatase, a pyrophosphatase, and certain *l*-peptidases in the rabbit lens. These substances were shown to possess a sensitivity to glutathione and ascorbic acid, which may be indicative of a physiologic relation. The phosphatases are very heat-labile as compared with most other enzymes. In eyes enucleated immediately after exposure to microwaves, pyrophosphatase was reduced in eyes of gross damage to the lens, but no reduction of enzymatic activity was noted when the lens appeared normal, although in such eyes cataract due to exposure to microwaves could be expected to develop within several days or weeks. There was no reduction in phosphatase activity in cases of posterior cortical cataract caused by microwaves, but in totally cataractous lenses the phosphatase activity was almost negligible.

Proteins.—It has been determined by Ten Cate [13] that within 60 to 74 hours chick embryos and 21-mm. Rana fusca embryos give a positive reaction with rabbit antisera produced by immunization with lens material from fowl and frogs. It appears, therefore, that adult-lens proteins are present at the time of development of the lens vesicle and that chemical differentiation precedes the morphologic differentiation of the lens fibers. Using a microbiologic technique, Schaeffer and Shankman [14] determined the amounts of certain amino acids in the human lens. They report significantly less histidine and more leucine and isoleucine than in animal lenses. No significant difference in the amino-acid content of the normal and the cataractous human lens was found. Merriam and Kinsey,[15] after their studies on the turnover of glutathione in the lens, investigated the interconversions

10. Ferrante, A.: Ricerche sulla glicolisi del cristallino, Ann. ottal. e clin. ocul. **76**:209-219, 1950.

11. Ely, L.: The Oxidation of Lactic Acid, Pyruvic Acid, and Various Members of the Citric Acid Cycle by Bovine Lens Homogenates, Am. J. Ophth. **34**: 127-130 (May, Pt. 2), 1951.

12. Daily, L., Jr.; Zeller, E.; Wakim, K.; Herrick, J., and Benedict, W.: Influence of Microwaves on Certain Enzyme Systems in the Lens of the Eye, Am. J. Ophth. **34**:1301-1306, 1951. Zeller, E.; Daily, L.; Wakim, K., and Herrick, J.: Contributions to the Enzymology of the Normal and Cataractous Lens, Proc. Staff Meet., Mayo Clin. **26**:194-199, 1951.

13. Ten Cate, G.: Presence of Adult Lens Protein in Young Lens Vesicles of Chicken and Frog Embryos, J. Cyto-Embryol. Belgo-Neerland., pp. 92-95, 1949. Ten Cate, G., and van Doorenmaalen, W. J.: Analysis of the Development of the Eye-Lens in Chicken and Frog Embryos by Means of the Precipitin Reaction, Proc. K. nederl. Akad. Wet. **53**:894-907, 1950.

14. Schaeffer, A., and Shankman, S.: The Amino Acid Composition of the Proteins of the Ocular Tissues, Am. J. Ophth. **33**:1049-1054, 1950.

15. Merriam, F., and Kinsey, V.: Studies on the Crystalline Lens: III. Incorporation of Glycine and Serine in the Proteins of Lenses Cultured in Vitro, Arch. Ophth. **44**:651-658 (Nov.) 1950.

of the amino acids and the turnover of lens protein. They utilized a technique in which lenses were incubated in vitro with glycine labeled with C^{14}. After hydrolysis of the lens protein, the component amino acids were separated by means of starch-column chromatography. Although it is possible for glycine to be associated with protein by linkages other than peptid bonds, the precautions taken would seem largely adequate to preclude this possibility, and the large amount of radioactive carbon found in the glycine fraction is therefore strongly suggestive of a turnover of glycine in the lens protein. A considerable amount of C^{14} was also found in the serine fraction, indicating the rapid conversion of glycine to this amino acid. Also presented is the amino-acid composition of rabbit lenses, as determined by the aforementioned procedures.

Sulfhydryls.—Dische and Zil [16] investigated the sulfhydryl content of the normal lenses of certain animals, as well as of the cataractous human lens. Glutathione was present in normal mammalian lenses in the reduced state in amounts varying from approximately 105 to 188 mg. per 100 cc., but was absent in the oxidized form. The cysteine content of the soluble proteins (crystallins) was considerably higher than the cystine content, the ratio varying from about 4:1 to 6:1. In the albuminoid, however, the cystine was in preponderance and amounted to approximately twice the cysteine. The total amounts of the two amino acids were higher in the soluble protein fraction than in the albuminoid, owing to the high SH content of β-crystallin. In the human cataractous lens the glutathione content was reduced from 60 to 80%. In the soluble protein fraction there was an inversion of the cysteine-cystine ratio, whereas the cysteine-cystine total remained essentially unchanged, indicating an oxidation of SH groups. In the albuminoid fraction the cysteine-cystine ratio was similarly diminished, the cysteine-cystine total increasing, however, and being accompanied with an absolute increase in the albuminoid. In another part of this study, dealing with partial cataracts, the authors show that the cysteine-to-cystine shift in the soluble protein fraction occurs in the cataractous, as well as in the noncataractous, portion of the lens. The increase in the cysteine-cystine total in the albuminoid fraction, however, was not observed in the noncataractous portion of the partially cataractous lens. In their evaluation of the foregoing data, the authors propose the following theory for the development of senile cataract: In the absence of a mechanism preventing SH oxidation, the soluble β-crystallin is oxidized to an insoluble protein. Possibly, opacities appear when, concomitant with this, there is a reduction in the glutathione below a certain critical level. They thus believe that the increase in albuminoid in the cataractous process may be explained by assuming that it originated in the β-crystallin fraction, rather than in the α-crystallin fraction, as heretofore supposed.

Congenital Anomalies

Congenital Cataract.—Lee and Benedict [17] describe a new pedigree of the central pulverulent type of hereditary nuclear cataract comprising 200 persons, of whom 63 were affected. Transmission conformed to the Mendelian law of domi-

16. Dische, Z., and Zil, H.: Studies on the Oxidation of Cysteine to Cystine in Lens Proteins During Cataract Formation, Am. J. Ophth. **34**:104-113 (May, Pt. 2) 1951.

17. Lee, J., and Benedict, W.: Hereditary Nuclear Cataract, Arch. Ophth. **44**:643-650 (Nov.) 1950.

nance, and the condition was stationary, never appreciably interfering with the visual acuity. The first symptom was appearance of a preference for subdued lighting at about the age of 2 years, and the authors suggest that while the cataract is present at birth, it does not reach its final, stationary form until the age of 2 years. The authors found that in a number of patients in the pedigree the nuclear opacity measured 4.5 mm. in diameter and was characterized by the appearance of a clear Y on its anterior aspect, both of which factors would seem to indicate involvement of the fetal, rather than the embryonic, nucleus.

François and Lambrechts [18] present an interesting pedigree, including seven generations, in which 37 of 117 persons showed cataractous changes. Transmission occurred as a dominant characteristic. In this pedigree a congenital posterior polar cataract was associated with a posterior cortical cataract, which appeared later in life.

Several cases [19] of micrognathia with bird-like facies are reported in association with cataract. Apparently, cataract constitutes an integral part of the syndrome, the cause of which Pau [19b] speculates may be due to trophic disturbances.

It has been known for more than 10 years that maternal rubella may produce in the fetus a number of malformations, of which cataract is one of the commonest. Recent reports [20] confirm the belief that the most dangerous period of pregnancy so far as the fetus is concerned is the first trimester; the percentages of defective children born to mothers with rubella during this period, however, appear to be somewhat lower than the percentages reported during the years of the Australian epidemic. Thus, Anderson [20c] found 22 defective fetuses, 6 of whom were affected with cataract, among a group of 44 women who contracted rubella in the first trimester, and Wiedemann [20d] states that only 30% of women in the first trimester are considered to have offspring with rubella embryopathy.

Ectopia Lentis.—A number of reports [21] on the dislocated lens have appeared, in the majority of which the defect was associated with arachnodactyly (Marfan's syndrome). In a study of 148 cases of congenital ectopia lentis collected from the files in Copenhagen clinics, Lund and Sjøntoft [22] found the most important complications to be glaucoma and retinal detachment. Whether or not the condition was hereditary did not affect the incidence of arachnodactyly and cataract. Retinal

18. François, J., and Lambrechts, J.: Cataracte polaire postérieure congénitale et évolutive a herédité dominante, Ann. ocul. **184**:423-432, 1951.

19. (*a*) Streiff, E.: Dysmorphie mandibulo-faciale (tête d'oiseau) et altérations oculaires, Ophthalmologica **120**:79-83, 1950. (*b*) Pau, H.: Vogelgesicht mit Permeabilitätskatarakt als Folge trophischer Störungen, Klin. Monatsbl. Augenh. **117**:529-532, 1950.

20. (*a*) Naccache, E., and Majdalani, E.: Rubéole maternelle et malformations congénitales multiples, Rev. med. moyen-Orient **7**:321-326, 1950. (*b*) Verger and Channarond: Deux cas d'embryopathie rubéoleuse, Arch. franç. pediat. **8**:339, 1951. (*c*) Anderson, S. G.: Epidemiological Aspect of Rubella, M. J. Australia **2**:389-390, 1950. (*d*) Wiedemann, H.: Angeborene Missbildungen nach Virus Infectionskrankheit der Mutter während der Schwangersehaft, Ärztl. Wchnschr. **5**:453-459, 1950.

21. Wettler, H.: Über einem Fall von Wernerschem Syndrom, Ophthalmologica **121**:172-174, 1951. Magni, S.: Aracnodattilia ed ectopia lentis, Riv. oto-neuro-oftal. **25**:73-106, 1950. Hudson, J. R.: Marfan's Syndrome with Retinal Detachment, Brit. J. Ophth. **35**:244-245, 1951. Sloboziano, H., and Gulesiu, T.: Contribution á l'étude des anomalies oculaires dans la dolichosténomélie, Arch. opht. **10**:500-504, 1950.

22. Lund, A., and Sjøntoft, F.: Congenital Ectopia Lentis, Acta ophth. **28**: 33-48, 1950.

detachment occurred exclusively in the nonhereditary group, and ocular malformation and glaucoma were more frequently encountered in the hereditary group. The ultimate outlook for useful vision was also more favorable in the hereditary cases. Mariotti [23] suggests that hypophyseal deficiency may be an etiologic factor in cases associated with arachnodactyly. Starke [24] considers the syndrome as a defective development of mesodermal structures.

Cataracts Associated with Endocrine Disturbances

Diabetes.—As the result of a study of 440 diabetic patients, which revealed the presence of true diabetic cataract in about 4%, Heinsius and Arndt [25] are of the opinion that the incidence of this cataract is considerably higher than is recognized at present. About one-fifth of their patients had coexisting tuberculosis. Patterson [26] studied an experimental diabetic cataract produced by the intravenous injection of dehydroascorbic acid and related compounds in rats. He states that the mechanism involves at least partial saturation of the renal-tubule reabsorption pathway for glucose. Since one or more substances of an essential nature may be reabsorbed via this same pathway, it is possible that the cataract develops on a deficiency basis. The onset of cataract formation was correlated with the severity of the diabetes, and it was found that when the blood sugar was high mature cataract developed in both eyes in 8 to 10 weeks. When the blood sugar was lower, cataract was slower to develop and was occasionally unilateral. In the opinion of the author, the inverse relationship between the time for development of cataract and the extent of hyperglycemia is best expressed by the equation for a hyperbola, rather than for a straight line.

Tetany.—Pau [27] reports the occurrence of cataract associated with corneal dystrophy in a woman aged 55 following several episodes of tetany, which were the sequela of overextensive thyroid surgery. The lenses showed posterior subcapsular opacities, as well as milky cloudiness of the nuclei. Although 11 years have elapsed, the cataracts have not matured, the author ascribing the retardation of the condition to successful therapy. Brand [28] describes a case of tetany cataract in which he found the calcium levels of the aqueous and the serum to be 8.2 and 2.3 mg. per 100 cc., respectively. He states that in tetany the calcium level of the aqueous is essentially unchanged and does not decrease with that of the blood. Therefore, hypocalcemia cannot be the etiologic factor in the development of the

23. Mariotti, L.: Contributo alla sindrome di Marfan (aracnodattilia ed ectopia della lente), con particulare riguardo alla sintomatologia oculare ed alla ereditarieta, Ann. ottal. e clin. ocul. **76**:361-372, 1950.

24. Starke, H.: Zur Pathogenese des Marfan-Syndroms, von Graefes Arch. Ophth. **151**:384-390, 1951.

25. Heinsius, E., and Arndt, G.: Über Häufigkeit des Vorkommens, Form, und Genese der echten diabetischen Katarakt und Katarakt bei Diabetes, von Graefes Arch. Ophth. **150**:555-571, 1950.

26. Patterson, J.: Course of Diabetes and Development of Cataract After Injecting Dehydroascorbic Acid and Related Substances, Am. J. Physiol. **165**:61-65, 1951.

27. Pau, H.: Hornhautdystrophie und Katarakt als Folge von Schilddrüsenexstirpation, Klin. Monatsbl. Augenh. **118**:75-78, 1951.

28. Brand, I.: Contribution to Data on the Pathogenesis of Tetany Cataract, Acta ophth. **28**:371-376, 1950.

cataract. He speculates that the cataract may result from certain hormone-induced changes in the permeability of the capsule which permit the passage of calcium into the lens.

Mongolism.—Spitzer and Mann [29] examined a group of mentally defective persons, including patients with mongolism and epilepsy, for evidence of abnormalities of the teeth and lens. Changes in the lens in the form of sutural cataracts, flake opacities of the coronary type, and arcuate opacities were found in all but 9 of the 83 patients examined. Of a series of 52 patients with mongolism, Lowe [30] found arcuate lens opacities within the fetal nucleus in 8. He believes these to be due to aberrant capsulopupillary vessels associated with other vascular anomalies common in persons with mongolism. Of 81 patients with mongolism, Skeller and Øster [31] found lens opacities in 46%.

Dermatitis.—A case of cataracta complicata in a child whose mother and other relatives had ichthyosis congenita and cuneiform lens opacities is reported by Jancke.[32]

Cataracts Produced by Toxins

Galactose.—Various substances when introduced into the animal body are capable of producing cataract, galactose being perhaps one of the better known experimental agents. Galactose cataract in man, however, is rare, only about a half-dozen cases being known, and it is of interest that two instances of this condition have been reported in the past year. This cataract occurs in association with a probably hereditary congenital anomaly of carbohydrate metabolism, galactosemia, in which the liver is apparently unable to convert galactose to glucose, permitting the accumulation of this substance in the blood, where it may exert a toxic effect on certain susceptible tissues, notably the lens. Systemic manifestations, not unlike those of the starvation syndrome, may appear within the first few months after birth. In other cases, perhaps of milder degree, symptoms may be entirely lacking, and the condition may go unrecognized for a number of years, when the appearance of a cataract draws attention to it. The diagnosis is made by the findings of galactosemia, galactosuria, and impaired galactose tolerance. Therapy consists in the institution of a galactose-free diet, and it is believed that if this is done sufficiently early, untoward changes may be reversed, or at least controlled. Falls [33] and associates present the case of a white girl aged 8 weeks in which examination revealed "a sharply outlined zonular area of increased density of an opalescent nebular nature just beneath the capsule in both lenses. In addition, it was evident that the nuclear areas were likewise somewhat opalescent in character." Enns [34] reports the case of a white boy aged 6 weeks in which he describes "an area of

29. Spitzer, R., and Mann, I.: Congenital Malformations in the Teeth and Eyes of Mental Defectives, J. Ment. Sc. **96**:681-709, 1950.

30. Lowe, R.: The Arcuate Lens Opacities of Mongolism and Cataracts of Similar Appearance, Brit. J. Ophth. **34**:484-488, 1950.

31. Skeller, E., and Øster, J.: Eye Symptoms in Mongolism, Acta ophth. **29**:149-161, 1951; abstracted, Am. J. Ophth. **34**:1646, 1951.

32. Jancke, G.: Cataracta syndermotatica and Ichthyosis congenita, Klin. Monatsbl. Augenh. **117**:286-290, 1950.

33. Falls, H.; Lowrey, G., and Anderson, W., Jr.: Galactosemia Cataract, Am. J. Ophth. **34**:1271-1274, 1951.

34. Enns, J.: Human Galactosemia Cataract, Am. J. Ophth. **34**:1268-1269, 1951.

diffuse homogeneous relucency entirely throughout the fetal and embryonal nuclei with a few scattered small brilliant white opacities." In the cortex there were noted small equatorial vacuoles. Approximately six months later, and apparently as a result of dietary management, in the second case the nuclear condition had undergone considerable regression, and the cortex was clear, whereas in the first case there was no appreciable change at the age of approximately 4 months, although similar therapy had been instituted.

Antihistamines.—Azzolini and Faldi [35] determined that certain antihistamine drugs of the amino-ethyl-aniline group are capable of producing cataract. Instillation and subconjunctival injections of the agents tried were without damaging results, but intraperitoneal injection in doses usually employed for other purposes resulted in sutural cataracts, which were apparently of a progressive nature.

LENTICULAR CHANGES DUE TO DEFICIENCIES

Morone [36] performed a series of experiments on rats designed to ascertain the effects of a low-protein and high-fat diet on the lens. Although the changes observed were minimal, there were noted increased prominence of the sutures, subcapsular opacities, and slight clouding of the nucleus. These changes were shown to be due to the inadequate protein content, rather than to the high-fat content, of the diet.

Radiation Cataract

X-Radiation Cataract.—The present emphasis on atomic warfare has stimulated a considerable amount of research on radiation cataract, and several methods for their experimental production in animals are now well known. Cogan and Donaldson [37] have recently reported on the production of x-ray cataract in a series of rabbits of various ages. They used radiations of 200 and 1,200 kv. in doses of from 250 to 3,000 r. The earliest clinical findings following irradiation were epilation of the lids and keratoconjunctivitis, both of which appeared within 15 to 35 days. The threshold doses were 1,500 and 1,000 r for the 1,200- and 200-kv. radiations, respectively, and the conditions were in general severer and of a shorter latent period with the higher doses and the lower kilovoltages. Age did not appear to affect the susceptibility to these conditions. With the exposure to 1,200-kv. radiations of 10-week-old rabbits, cataractous changes appeared in about one month when the dose was between 1,500 and 3,000 r and in approximately three to five months when the dose was 250 to 1,000 r. The latent period for the development of cataract was found to be greatly influenced by the age of the animal in that younger animals showed a greater susceptibility.

In this series, with doses less than 1,000 r, cataract began with the appearance of vacuoles and granules in the region of the horizontal suture line. With the

35. Azzolini, U., and Faldi, S.: Cataratta sperimentale da preparati antistaminici di sintesi, Boll. ocul. **30**:129-134, 1951; abstracted, Am. J. Ophth. **34**:1466, 1951.

36. Morone, G.: Sul comportamento del cristallino in ratti sottoposti a diete ipoproteiche e iperlipidiche, Rass. ital. ottal. **19**:209-223, 1950.

37. Cogan, D., and Donaldson, D.: Experimental Radiation Cataracts: I. Cataracts in the Rabbit Following Single X-Ray Exposure, A. M. A. Arch. Ophth. **45**: 508-522 (May) 1951.

higher doses, larger vacuoles appeared at the ends of the suture, and were accompanied with a collarette of opacities in the extreme periphery. Von Sallmann,[38] using 220 kv. x-radiations and a dose of 2,000 r, states that the first ophthalmoscopically visible changes occurred near the equator, where a fine dark ring could be seen. The appearance of this ring was rapidly followed by the formation of clusters of vacuoles, often in the form of a ring, at a greater distance from the equator, in the posterior cortex. Divided doses increased the latent period. Both Cogan and Donaldson and von Sallmann were able to recognize evidence of cytologic disorganization in the equatorial region prior to the earliest ophthalmoscopic signs. According to von Sallmann, the order of progression of the cellular changes was as follows: a displacement of nuclei in the lens bow and disordered appearance of the nuclei in the preequatorial region (two weeks); loss of the palisade arrangement at the equator and swelling and change in the angulation of the youngest, most peripheral lens fibers (three weeks), and vacuolation (four weeks). It is usually presumed that changes in the lens fibers result from damage to their nuclei; yet von Sallmann noted a number of instances in which the pathologic changes at the posterior subcapsular ends of the lens fibers were very severe, as compared with the slighter changes in the nuclei of the bow and preequator, so that the possibility of a direct radiation effect on the cytoplasm which was secondarily detrimental to the nuclei could not be precluded.

Proceeding on the theory that irradiation produces chemical changes within the cell (blocking of desoxyribosenucleic acid) which eventually result in the pathologic condition of cataract, von Sallmann, by means of a qualitative staining technique, investigated the amounts and degree of polymerization of the important nuclear constituent desoxyribosenucleic acid. In the normal animal he demonstrated a comparatively large amount of the highly polymerized acid in the germinating nuclei of the preequatorial zone. He was unable to show conclusively, however, that a diminution in the desoxyribosenucleic-acid content and in the degree of polymerization definitely preceded structural deterioration within the nuclei.

In another paper, von Sallmann and associates[39] report on a series of experiments in which they tested the value of certain protective substances in the prevention of the ocular effects of irradiation. The right eyes of a group of rabbits were exposed to x-radiation of 200 kv. in a dose of 1,500 r. Immediately after this, cysteine was administered intravenously. Thirty minutes later the left eye was irradiated, the same factors being used as in the right eye. No protection was observed in the eyes first irradiated (right eyes), but in the left eyes the epilation effect was greatly reduced and the development of lens opacities was either completely prevented or was minimal. The intraperitoneal injection of cysteine and the iontophoretic administration of cysteine and of sodium cyanide were not effective in preventing the damaging effects of radiation.

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38. von Sallmann, L.: Experimental Studies on Early Lens Changes After Roentgen Irradiation: I. Morphologic and Cytochemical Changes, A. M. A. Arch. Ophth. **45**:149-164 (Feb.) 1951.

39. von Sallmann, L.; Dische, Z.; Ehrlich, G., and Munoz, C.: Study on Penetration of Cysteine and Cystine into Aqueous Humor of Rabbits and Its Relation to Early X-Irradiation Effects on the Eye, Am. J. Ophth. **34**:95-103 (May, Pt. II) 1951

Neutron Cataract.—Krause and Bond [40] make a valuable review of the clinical and experimental investigations of x-ray and neutron cataract. They stress the basic similarity of the pathologic processes in the two conditions. They state that neutrons produce more damage per unit of absorbed energy than do x-rays and that this probably results in a shorter latent period. Barron's work on the oxidation of sulfhydryls by irradiation and the resultant effect on the enzyme systems of the lens is discussed, and this phenomenon is proposed as a possible mechanism in the formation of cataract.

The first histopathologic study of an atom-bomb radiation cataract is reported by Kimura and Ikui.[41] At the time of the blast their patient was on a streetcar at an estimated distance of 780 meters from the hypocenter. Within two hours the acute symptoms of radiation sickness began, and on the 14th day the scalp hair began to be lost, with resulting total baldness the next few days. About two years later vision began to fail. Four years after exposure vision in the right eye was 20/30 with correction, and examination revealed an irregular, disc-shaped posterior polar opacity of a lace-like nature and interspersed with a few vacuoles. In the left eye the visual acuity was 20/50 with correction, and the opacity, although similar to that in the right eye, appeared larger and denser. Its greater peripheral density gave it a doughnut-like appearance when viewed with the ophthalmoscope, while with the slit lamp it appeared planoconvex, the surfaces containing many polychromatic particles and reflecting light brightly. After successful intracapsular extraction of the lens in the left eye, pathologic studies revealed changes similar to those seen in x-radiation cataract. No normal lens fibers could be found peripheral to the opacity; for this reason the authors suggest that the progression of the opacity is dependent upon irreversible changes in the epithelial cells as a result of the irradiation.

Wilder and Maynard [42] also report that the ocular changes occurring as a result of irradiation from atomic fission are similar to those resulting from x-irradiation. They state that vacuolation of the lens may be due to severe anemia, although total cataract is undoubtedly the result of the irradiation.

Electricity.—In a patient who was severely burned after accidental exposure to a high-voltage electric current, Starke [43] reports the development of an electric cataract, accompanied with cystic degeneration of the retina.

Heat.—It has been known for several years that experimental cataract could be produced by exposure to 12-cm. microwaves and that this effect is apparently a thermal one. Recently, Richardson and co-workers [44] investigated the action of 3-cm. microwaves on the eye and concluded that, although damage to the human eye is possible in certain radar workers, it is not at all likely if reasonable precautions are observed.

40. Krause, A. C., and Bond, J. O.: Neutron Cataracts, Am. J. Ophth. **34**:25-35, 1951.

41. Kimura, S., and Ikui, H.: Atomic-Bomb Radiation Cataract: Case Report with Histopathologic Study, Am. J. Ophth. **34**:811-816, 1951.

42. Wilder, H., and Maynard, R.: Ocular Changes Produced by Total Body Irradiation, Am. J. Path. **27**:1-20, 1951.

43. Starke, H.: Über bisher unbekannte Augenhintergrundsveränderungen nach Starkstromverletzung, Klin. Monatsbl. Augenh. **117**:249-253, 1950.

44. Richardson, A.; Duane, T. D., and Hines, H.: Experimental Cataract Produced by Three Centimeter Pulsed Microwave Irradiations, A. M. A. Arch. Ophth. **45**:382-386 (April) 1951.

Doubt has again been cast on Vogt's theory that glass blower's cataract is due to the damaging effects of infrared radiation. Goldmann and co-workers,[45] using a photometric method, showed that the lenses of several species, including man, absorb less infrared rays than does water. Dunn [46] investigated the incidence of cataract resulting from exposure to infrared rays among workers producing borosilicate glass products by hand. None was found in a series of workers who had been actively engaged in this occupation for over 30 years.

Cataracts Due to Senile Changes and Miscellaneous Factors

Pau [47] has made several reports on his investigations of nuclear cataract occurring in old age. In one experiment he weighed the crystalline lenses removed from cadavers of ages ranging from 42 to 87 years. In cases of nuclear cataract the size of the nucleus was above average. He found the weight of the nucleus in supranuclear cataract to be very variable as a result of the induration and the reduction in the size of the nucleus. In another report,[48] he expresses the opinion that nuclear cataract is frequently a condition associated with generalized deterioration of the globe, occurring concomitantly with such diseases as glaucoma, diabetic retinitis, myopia, chronic iritis, and amblyopia. In 10 patients with cataract, each displaying one of the aforementioned conditions, the eye most severely involved with the particular type of cataract was the one in which a brunescent cataract was present, while the least affected or normal eye showed less severe or minimal changes in the lens. In another report, Pau and Stüttgen [49] describe a series of chemical studies designed to investigate the brown pigment of the sclerotic nucleus.

Pau [50] expresses the opinion that coronary cataract, which is usually considered a presenile type, may be related to traumatic cataract. He describes a case of unilateral coronary cataract and suggests that the clearness of the other lens was due to an accommodative paralysis existing on that side. He mentions another case of coronary cataract with absence of opacities in the region of a coloboma of the iris where the zonule fibers were absent. He suggests that zonular pull in certain predisposed persons is the etiologic factor in formation of this cataract. In this connection, Werner [51] writes of the angular deformity produced by the pull of the zonular fibers in the hyalocapsular recess, now seen with the use of Goldmann's new three-mirror contact lens. Bignell [52] interprets folds in the lens capsule seen after trauma as being due to a partial zonular rupture.

45. Goldmann, H.; Koenig, H., and Madder, F.: Die Durchlassigkeit der Augenlinsen für Infrarot, Ophthalmologica **120**:198-205, 1950.

46. Dunn, K.: Cataract from Infra-Red Rays (Glass Workers' Cataract): A Preliminary Study on Exposures, A. M. A. Arch. Indust. Hyg. **1**:166-180 (Feb.) 1950.

47. Pau, H.: Beiträge zur Kataraktgenese, von Graefes Arch. Ophth. **150**:340-357, 1950.

48. Pau, H.: Die Cataracta nuclearis (brunescens) als Zeichen einer degenerativen Bulbusveränderung, Klin. Monatsbl. Augenh. **119**:12-16, 1951.

49. Pau, H., and Stüttgen, G.: Probleme der Linsenphysiologie, von Graefes Arch. Ophth. **151**:343-351, 1951.

50. Pau, H.: Ätiologische Betrachtung zur Cataracta coronaria, Klin. Monatsbl. Augenh. **117**:290-295, 1950.

51. Werner, H.: Biomikroskopische Untersuchungen über den Ansatz der hintern Zonulafasern an der Linse, Ophthalmologica **120**: 47-49, 1950.

52. Bignell, J.: Case Notes: Folds in the Lens Capsule After Trauma: A Sign of Partial Rupture of the Zonule, Brit. J. Ophth. **35**: 226-231, 1951.

Soemmering's ring, one of the forms of after-cataract, is discussed by Guha.[53] He states that its tendency to dislocate is due to myopia, degenerative changes, trauma, or spontaneous factors.

The formation of cataract in patients with middle-ear disease is relatively frequent, according to Marchesani and Koch.[54] They suggest that a relation exists between cataract and a disturbance of the auriculo-ocular sympathetic pathways.

Simonelli and Azzolini[55] report on studies similar to those of Legrand, who found punctate opacities in the lenses of patients with pulmonary tuberculosis. These opacities, which are found in both the cortex and the nucleus, are believed to be due to a calcium deficiency in the aqueous. Of a series of about 100 patients with pulmonary tuberculosis, lenticular opacities occurred in about 90%. Vision, however, was unimpaired.

Pathologic alteration in the lens as a cause of secondary glaucoma has been considered by Bonavolontà[56] and by Rychener.[57] In his classification, the latter includes intumescent cataract, hypermature or Morgagnian cataract, exfoliation of the lens capsule, and subluxation of the lens. Lens extraction is a satisfactory treatment in all types with the exception of exfoliation of the lens capsule.

Lens opacity occasionally follows certain surgical procedures for glaucoma. Magni[58] is of the opinion that this type of cataract is due to capsular injury from the freeing of posterior synechia at the time of operation. Since posterior synechia may accompany the prolonged use of miotics, he cautions against the unnecessary delay of operation for glaucoma. Auricchio[59] studied the susceptibility of persons with high myopia to cataract formation. He suggests that the degenerative process in the choroid and retina causes an alteration in the physiochemical composition of the fluids bathing the lens, which change, in turn, predisposes to lens opacities.

Cataract Surgery

Preparation of the Patient.—Poyales[60] stresses the importance of reducing the bacterial flora of the external eye to a minimum at the time of operation and recommends for this purpose the application of penicillin ointment several days prior to the operation. Snyder[61] warns that a definite increase in the intraocular tension occurs when the edentulous patient swallows. He suggests, therefore, that when possible the dentures remain in place during the operation. The special

53. Guha, G.: Soemmering's Ring and Its Dislocations, Brit. J. Ophth. **35**:226-231, 1951.

54. Marchesani, O., and Koch, H.: Katarakt bei Mittelohrerkrankungen, von Graefes Arch. Ophth. **150**:329-339, 1950.

55. Simonelli, M., and Azzolini, U.: Sulla frequenza di opacità del cristallino in soggetti tubercolotici, Gior. ital. oftal. **3**:401-404, 1950.

56. Bonavolontà, A.: Sul glaucoma secondario a cataratta ipermatura, Rass. ital. ottal. **19**: 326-347, 1950; abstracted, Am. J. Ophth. **34**: 666, 1951.

57. Rychener, R. O.: Secondary Glaucoma Due to Cataract, Am. J. Ophth. **33**:1666-1669, 1950.

58. Magni, S.: La comparsa di cataratta dopo intervento di sclera-iridectomia anti glaucomatosa per adesione dell iride alla capsula del cristallino, Boll. ocul. **29**:685-690, 1950.

59. Auricchio, G.: Studi sulla cataratta complicata, Rass. ital. ottal. **20**: 8-14, 1951; abstracted, Am. J. Ophth. **34**:1631, 1951.

60. Poyales, A.: Consideraciones sobre la extraccíon del cristalino, Arch. Soc. oftal. hispano-am. **10**: 796-803, 1950.

61. Snyder, H.: A Warning About Lens Extraction in the Edentulous Patients, J. M. Soc. New Jersey **47**:289, 1950.

precautionary measures to be taken in the preoperative and postoperative periods of cataract surgery in the case of the diabetic patient are discussed by Heinsius and Götze.[62]

Curare.—Cordes and Mullen [63] and Farquharson [64] used curare as an adjuvant to local anesthesia in series of 85 and 70 cases, respectively. Although curare is no substitute for a good anesthetic, the temporary paralysis of the extraocular and palpebral muscles and the apparent sedative effect it affords make the procedure of cataract extraction a safer one. Cordes and Mullen are coming to the conclusion that it should be used with every cataract extraction, since it is impossible to predict every case in which difficulty may arise. It should be administered only by an anesthesiologist thoroughly acquainted with its dangers and limitations, and in such hands the remote chance of untoward reaction is greatly outweighed by the benefits obtained. Farquharson recommends that the dose employed should be minimal, but enough to insure maximum effect at the time the cataract is extracted. Initially, 1 cc. is administered. After three or four minutes, a second dose, of 0.5 to 1 cc., is injected and, if necessary, may be repeated. Oxygen must be ready in case its need should arise.

Operative Techniques.—Considerable variation still exists in the actual operative technique of cataract extraction. Hudson [65] reports excellent results with Kirby's method in a series of 60 intracapsular extractions. Gill [66] obtained good results in a smaller series, in which the incision was made with the keratome and the patient was allowed out of bed on the day following operation. Schulte [67] uses a Graefe knife and suggests that after contrapuncture the knife be manipulated as in Smith's method. Hruby [68] favors the placement of traction sutures through the tendons of the four rectus muscles as a means of preventing vitreous complications. In his series of 646 intracapsular extractions, such complications were reduced from about 18% to 8%. He believes that, in addition, these sutures may increase the tension on the zonule fibers, making their rupture somewhat easier. Hartmann [69] recommends that the chamber be restored immediately after operation by the injection of air, but cautions that if an excessive amount is injected it may gain access to the posterior chamber and push the iris forward.

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62. Heinsius, E., and Götze, R.: Zur Allgemeinbehandlung von Diabetikern während des Klinikaufenthaltes bei Kataraktoperationen, Klin. Monatsbl. Augenh. **117**:270-274, 1950.

63. Cordes, F., and Mullen, R.: Use of Curare in Cataract Surgery, Am. J. Ophth. **34**:557-563, 1951.

64. Farquharson, H.: Curare with Local Anesthesia in Cataract Surgery, Am. J. Ophth. **34**:554-556, 1951.

65. Hudson, J. R.: Intracapsular Extraction by Kirby's Technique, Brit. J. Ophth. **35**:284-290, 1951.

66. Gill, E. G.: Advances in Cataract Surgery, Eye, Ear, Nose & Throat Monthly **30**:191-196, 1951.

67. Schulte, D.: Erleichterung der Schnittführung zur Starextraktion, Klin. Monatsbl. Augenh. **117**:198-200, 1950.

68. Hruby, K.: Vorschlage zur Staroperation, Klin. Monatsbl. Augenh. **119**:121-135, 1951.

69. Hartmann, E.: L'injection d'air dans la chambre antérieure après extraction du cristallin, Ann. ocul. **183**:64-65, 1950.

In an evaluation of the round-pupil method versus the combined method of cataract extraction, Carter [70] concludes that the former has many advantages over the latter and is no more hazardous. The cosmetic result is desirable, especially in cases of unilateral cataract, as the optical result is theoretically better because of the smaller diffusion image falling on the retina. The fact that the iris remains intact acts to prevent the presentation of vitreous, diminishes the necessity for later manipulation of the iris, and lessens the possibility of hemorrhage in patients with vascular disease. Prolapse of the vitreous and iris were found to be less common in the round-pupil extraction; iritis and postoperative glaucoma were slightly commoner, however. The incidence of hyphema was about the same in the two procedures. Larsen's [71] analysis of round-pupil extractions and extractions with iridectomy agrees with that of Carter's for the most part; in addition, it suggests that a better visual acuity may be achieved with the round-pupil extraction.

In a valuable paper on the dynamics of erysiphake extraction, Harrington [72] discusses the mechanism of phakoerysis and its advantages over the commoner methods of intracapsular extraction. He has demonstrated experimentally that after the application of the suction cup to the anterior capsule of a normal or soft lens, the capsule is drawn forward into the cup with the exertion of uniform traction on the equatorial region, causing that portion of the capsule to move forward onto the anterior surface of the lens. Thus, an even stress is created on the zonule fibers, which draws them taut and in a position tangential to the lens equator, so that the slightest movement of the erysiphake shears them from the lens. In contrast to the forceps-and-external-pressure technique, phakoerysis does not involve the utilization of a wedge of vitreous; the stress is more uniformly applied and over a greater area, and the site of maximum stress, and therefore potential rupture of the capsule, is at the posterior pole. The erysiphake has the advantage over the forceps in that it is less likely to tear the capsule, and if it should slide off it may be reapplied without having adversely affected the outcome of the procedure. It may be successfully applied to the lens in which the capsule has been torn by forceps. If the capsule is delivered alone, the lens may be expressed, as in an extracapsular operation.

In general, all types of cataract may be extracted by the erysiphake, with the exception of a dislocated lens in which vitreous has presented in front of the lens. The function of the instrument and the technique of extraction, however, vary with the type of cataract. In the case of an ordinary immature soft cataract, slight traction on the erysiphake is all that is required to dislocate the lens. In the case of a hard nuclear cataract, the lens substance does not easily mold into the suction cup, and the limited zonular stress thus produced may be insufficient to cause zonular rupture. In such cases the erysiphake serves primarily as a fixation instrument, and external pressure may be needed to dislocate the lens. Phakoerysis is the preferred technique in cases of intumescent or hypermature cataract and in cases of exfoliation of the lens capsule. The difficulties encountered with the capsule forceps in these types is well known, and the fact that dislocation must be

70. Carter, L. F.: Round-Pupil Cataract Extraction, Am. J. Ophth. **34**:1108-1114, 1951.

71. Larsen, V.: Quelques considérations sur l'extraction de la cataracte, Acta ophth. **29**: 3-24, 1951.

72. Harrington, D. O.: Dynamics of Phakoerisis, Am. J. Ophth. **34**:1395-1402, 1951.

accomplished almost entirely by external pressure alone increases the dangers of the operation. Although with the proper use of the erysiphake capsular rupture seldom results, it may occur, especially with intumescent cataract, if too strong a vacuum is used or if an intumescent lens is extracted through a corneal section of insufficient size. As a result of recent modifications in the erysiphake which allow the surgeon direct control of the degree of vacuum, as well as the addition of a solid handle with which to manipulate the needle attaching to the suction cup (Harrington), phakoerysis has become a safe and convenient method of cataract extraction, as well as an indispensable one for dealing with the intumescent lens. Pallares [73] gives a favorable account of the use of the Moreno suction tip as an aid in phakoerysis.

Closure of Wound.—Tower [74] has contrived a device by means of which the wound may be rapidly closed within a matter of seconds after the extraction should the necessity arise. A small hook is soldered to whatever instrument is selected for the extraction (a muscle hook in the case of an intracapsular procedure), the suture ends being threaded through this hook, so that raising of the instrument automatically tightens the suture and produces apposition of the wound edges. For closure of the incision, Thorpe [75] recommends a suturing technique in which a semicircular trough which does not penetrate the entire cornea is made in a line concentric with the limbus and about 1 mm. behind it. The McLean sutures are placed, and the trough is perforated with a keratome. Fralick [76] advises that a 6-0 mild chromic surgical suture U. S. P., which is nonirritating to the tissues, be used. This suture will keep the edges approximated for four to five days, at which time the fibrous union is sufficiently strong.

In experiments designed to study the mechanism of healing following cataract incision, Dunnington [77] studied cataract incisions in rhesus monkeys with and without conjunctival flaps and using appositional corneal and corneoscleral sutures. In general, the author substantiated the earlier reports of Purtscher and Maggiore. In the absence of a conjunctival flap, an anterior-epithelium plug formed readily and was well developed at the end of 48 hours. When a conjunctival flap was present, the episcleral tissues assumed the chief role in the healing process, with only minimal participation by the deeper structures. No doubt remains that the limbal incision combined with a conjunctival flap should be used routinely in cataract extraction. Dunnington states that "the highly vascular nature of episcleral tissue causes prompt closure of the anterior part of the wound, while the conjunctival covering tends to prevent epithelium from growing between the edges of the incision." Minor faults in the approximation of the wound edges were not

73. Pallares, J.: Resultados de la extraccion intracapsular de la catarata con la ventosa de moreno, Arch. Soc. oftal. hispano-am. **11**:724-732, 1951; abstracted, Am. J. Ophth. **34**:1632, 1952.

74. Tower, P.: Rapid Closure of Wound in Cataract Extraction, Am. J. Ophth. **34**:1316-1317, 1951.

75. Thorpe, H.: A New Cataract Suture, Tr. Am. Acad. Ophth. **55**:289-291 (Jan.-Feb.) 1951.

76. Fralick, F.: 6-0 Chromatized Gut in Wound Closure After Cataract Extraction, West Virginia M. J. **46**: 251-255, 1950.

77. Dunnington, J. H.: Healing of Incisions for Cataract Extraction, Am. J. Ophth. **34**:36-45, 1951.

uncommon and, in the author's opinion, are responsible for many of the complications usually attributed to lack of cooperation on the part of the patient. In the presence of a flap, anterior gaping of the wound edges, due to excessively deep suturing, leads to the production of a large, highly vascularized episcleral plug, which predisposes to hemorrhage into the anterior chamber. Posterior gaping, on the other hand, is apt to lead to aqueous leakage and the formation of a cystoid cicatrix.

Complications.—In a series of 75 cases of cataract extraction in one-eyed patients, Callahan [78] found that, with the exception of corneal dystrophy, the complications that resulted in the loss of the first eye after operation could usually be avoided in the second eye.

Schepens [79] made a careful study of retinal detachment in aphakic eyes and found, in contrast to the usual equatorial changes seen in phakic eyes, a predisposition to detachment at the ora serrata in aphakic eyes. The poorer prognosis for detachment in eyes with aphakia very likely follows the difficulty attendant on an adequate examination of that area. The author calls attention to the difficulty of making the diagnosis early because the detachment is frequently flat and smooth in aphakic eyes. This condition, termed subclinical detachment, may precede an actual detachment for a considerable period. The occurrence of massive vitreous retraction, present in 45% of the cases in this series, is another important factor in the poorer prognosis. Of the types of cataract occurring in this series prior to detachment, posterior cortical opacities were present in 47%, posterior cortical opacities in the fellow eye in 24%, nuclear sclerosis or wedge-shaped opacities in 21%, and other pathologic conditions of the lens in about 8%. The detachment appeared within 3 months after operation in 21%, within 1 year in 18%, and within 18 years in 38%. In 21% the detachment was present prior to cataract extraction. The percentage of reattachments in aphakic and phakic eyes is of the same order, provided that one discounts the instances in which massive vitreous retraction occurs.

Loss of vitreous is a frequent complication of intracapsular extraction. Hartmann [80] states that scleral pressure, driving the vitreous to the front, is the chief reason for the loss. He believes that if the zonule fibers are ruptured by lateral pressure on the cornea or under direct observation, as in Kirby's method, vitreous loss can be minimized. There was no loss of vitreous in Hudson's series of 60 cases in which Kirby's technique was used.

Hemorrhage is one of the commoner complications following cataract surgery. According to Cosmetatos,[81] syphilitic patients are very likely to present this complication. It was also apparently more frequent during the occupation in Greece, when malnutrition was prevalent. In his series of 1,382 cataract operations,

78. Callahan, A.: Cataract Extraction in the One-Eyed Patient, South. M. J. **44**:179-188, 1951.

79. Schepens, C.: Retinal Detachment and Aphakia, A. M. A. Arch. Ophth. **45**:1-17 (Jan.) 1951.

80. Hartmann, E.: La perte de vitré au cours de l'extraction intra-capsulaire de la cataracte, Ann. ocul. **183**:545-562, 1950.

81. Cosmetatos, G.: Operative and Postoperative Complications of Cataract, Bull. Soc. hellen. ophth. **17**:233-244, 1950: abstracted, Excerpta Med., Sect. XII, **5**:368, 1951.

Sédan [82] enumerates the predisposing causes of hemorrhage as being loss of vitreous, diabetes, azotemia, hemorrhagic diatheses, severe hypertension, and the use of epinephrine. Expulsive hemorrhage has been reported by a number of authors. It occurred 9 times in Linnen's [83] series of 1,356 extractions. He speculated that the immediate cause may be sympathetic stimulation of the ocular vessels, which results in vascular congestion. He found that patients with hypertension, glaucoma, and high myopia seemed to be predisposed. Jayle and co-workers [84] cite a case of expulsive hemorrhage in which vascular fragility was present, but in which the inciting cause appeared to be an increase in the arterial blood pressure. Siegert [85] believes that a meteorologic factor may be implicated in the causation.

Leahey [86] reports on the bullous keratitis which may result from contact of a herniated vitreous with the posterior surface of the cornea after cataract extraction. The factors influencing the development of such a condition include "the location, duration, and density of the contact and the condition of the corneal endothelium at this area of contact." Treatment consists in the performance of posterior sclerotomy for the release of vitreous, freeing of the vitreous from the cornea, and the injection of an air bubble into the anterior chamber.

The curvature of the posterior surface of the cornea after cataract extraction was studied by Alajmo [87] in five cases employing Nordenson's method, as simplified by Berg. As was expected, the posterior and anterior surfaces of the cornea showed a reduction of the vertical curvature. Thus, the inverted astigmatism of the anterior surface is to some extent neutralized by the direct astigmatism of the posterior surface.

Surgery of Congenital Cataract.—Chandler [88] and Cordes [89] both make comprehensive reports on the surgery of congenital cataract. It has long been recognized that the postoperative prognosis for such cataracts is far less satisfactory than that for senile cataracts, and Cordes states that in only 50% of cases is postoperative vision of 20/200 or better achieved. Poor postoperative results are due to the increased incidence of surgical complications in cases of congenital cataract, as well as to the presence of ocular defects in approximately one-half of all cases. In view of the uncertainty with which the operation is fraught, Cordes and

82. Sédan, J.: Les hemorragies post-opératoires de la cataracte, Ann. ocul. **184**:1-16, 1951.

83. Linnen, H. J.: Über das Auftreten der expulsiven Blutung bei Staroperationen, Klin. Monatsbl. Augenh. **117**:275-286, 1950.

84. Jayle, G. E.; Berard, P. V., and Jacquenoud, P.: Un cas d'hémorragie expulsive au cours d'une intervention pour cataracte traite avec succes par sclerotomie postérieure, Bull. Soc. ophth. France, pp. 48-50, Jan., 1951.

85. Siegert, P.: Meteorische Auslösbarkeit expulsiver Blutungen, Klin. Monatsbl. Augenh. **118**:472-476, 1951.

86. Leahey, B. D.: Bullous Keratitis from Vitreous Contact, A. M. A. Arch. Ophth. **46**:22-32 (July) 1951.

87. Alajmo, A.: Ricerche sulla curvatura della superficie posteriore della cornea negli operati di cataratta, Gior. ital. oftal. **3**:439-449, 1950.

88. Chandler, P.: Surgery of the Lens in Infancy and Childhood, A. M. A. Arch. Ophth. **45**:125-138 (Feb.) 1951.

89. Cordes, F. C.: Evaluation ot the Surgery of Congenital Cataract, A. M. A. Arch. Ophth. **46**:132-144 (Aug.) 1951.

Chandler both agree that, in general, surgical intervention is not indicated if the visual acuity is 20/50 or better. According to Chandler, there is no question but that surgery is indicated in cases of bilateral complete cataract or in cases of partial, yet severe bilateral involvement. When the involvement of the lens is severe in one eye but only mild in the other, operation is indicated only when the better eye has vision of less than 20/50. In the case of bilateral dense central opacities in which satisfactory vision may be obtained with dilation of the pupil, surgery can usually be delayed for some time, although it may become necessary, particularly if the vision with small pupils is less than 20/50. When there is moderate involvement of both eyes, operation should not be performed if the vision is 20/50 or better under all conditions. In borderline cases, the extent to which the handicap interferes with the child's general development is an important consideration, and in such cases operation may be delayed at least until the child starts school, since amblyopia will not develop.

As to the most favorable age for surgery, difference of opinion still exists. Chandler is not adverse to operating on patients under the age of 1 year, and Cordes routinely operates on the first eye at the age of 6 months and the second eye sometime in the third year.

In Cordes' opinion, the operation of choice for the average soft cataract is linear extraction. If the pupil dilates widely, a simple extraction, as described by Barkan, should be done, whereas if dilation is poor, linear extraction combined with a full iridectomy is indicated. Chandler favors a modified form of this procedure but is of the opinion that it should be combined with a peripheral iridectomy, even in cases in which the pupil dilates well. Because of the minimal complications involved, Chandler appears to favor the procedure of optical iridectomy in certain cases of borderline vision in which the patient is handicapped by a small pupil. Cordes, on the other hand, speaks disparagingly of the results of this operation, particularly if performed late, and believes that there is little justification for it, since other procedures offer greater opportunities for good vision. The surgical procedure finally decided upon depends on a careful evaluation of the particular case, as well as the limitations and the experience of the operator. The importance of the use of mydriatics after all types of congenital-cataract surgery cannot be overemphasized.

Glaucoma and detachment of the retina are two rather common complications of congenital-cataract surgery that deserve special consideration. Chandler believes that glaucoma most often results from pupillary blockage by vitreous and the presentation of vitreous in the anterior chamber. The complication is most frequent after discission and is preventable provided one follows von Graefe's advice, "Never do a needling in the presence of a small pupil," and provided care is taken to disturb the vitreous as little as possible with the discission needle. Unfortunately, knowledge of the factors involved in detachment leaves much to be desired, and it is a not uncommon late sequel to cataract extraction. It is certainly wise, as Chandler states, to bear in mind that retinal detachment may occur if the vitreous is unduly disturbed; yet it is his opinion that the surest way to escape its disastrous consequences is to forego operation for the cataract in the first place. It is with this complication in mind that surgery is advised against in eyes with vision of 20/50 or better.

Surgery of Ectopia Lentis.—In congenital dislocation of the lens, Chandler [88] stresses that operation should not be considered unless the corrected vision is 20/70 or less. Since it is seldom possible satisfactorily to evaluate the visual acuity until the age of 5 or 6 years, it may be necessary to delay operation until this age is reached. For this condition Chandler recommends a procedure in which the lens is fixed with one needle and "stirred up" in the region of the equator opposite the direction of dislocation with another. This technique causes a shrinkage of the lens, enlarging the aphakic part of the pupil. In many cases one, and in nearly all cases two, such needlings will suffice to produce an adequately large aphakic pupil. Surgical intervention is not indicated in cases of posterior dislocation in which the lens is entirely out of the pupillary space or in which a small, but adequate, pupil permits aphakic vision. In cases of microphakia with anterior dislocation of the lens, an ensuing glaucoma as a rule is best treated by lens extraction. This is particularly true if slit-lamp examination reveals that the zonular attachments are largely absent. If, however, the zonular fibers are relatively intact, and if, for other reasons, the hazards of extraction in the particular case are deemed too great, a peripheral iridotomy or iridectomy is recommended. This technique prevents the blockage of the pupil by the lens, since pressure cannot build up in the posterior chamber to push the lens forward.

McDonald and Purnell [90] present their operative results in subluxated and luxated lenses in 114 eyes of patients ranging from infancy to old age. The incidence of secondary glaucoma as a complication was high, retinal detachment being the second most frequent complication. Through no fault in technique, the visual outcome was often disappointing, particularly so in cases in which the dislocation was due to trauma. The prognosis was slightly better in cases of dislocation due to secondary causes, such as uveitis. Operation was the least difficult, and was followed by the fewest complications, in the group with congenitally dislocated lenses.

Surgery of Cataract Following Uveitis and Glaucoma.—Papoloczy [91] emphasizes that, in spite of poor light perception, the possibility of a favorable result is not precluded in cases of "cataracta uveitica" and of cataract of the glaucomatous eye. However, the operation should be delayed for a sufficiently long time after the inflammation has subsided that inflammation may not recur. In glaucomatous eyes if the tension is greater than 30 mm. of mercury, glaucoma surgery should precede the cataract extraction. As a rule it is advisable to use the intracapsular method of extraction.

In children with bilateral uveitis, often an accompaniment of Still's disease (multiple rheumatoid arthritis), the development of cataract may necessitate surgery. Although it would be preferable to operate during a remission of the uveitis, this is not always possible, since in some cases a slight aqueous flare is never absent. Chandler [88] states that an intracapsular extraction is indicated in these cases regardless of the age of the patient, and the outcome is usually satisfactory, even though slight evidence of the uveitis may persist for many years.

90. McDonald, P. R., and Purnell, J. E.: The Dislocated Lens, J. A. M. A. **145**:220-226 (Jan. 27) 1951.

91. Papoloczy, F.: Modifications of Operative Methods After Complicated Cataracts, Am. J. Ophth. **34**:895-897, 1951.

VITREOUS HUMOR

Chemistry and Structure.—Schaeffer and Murray [92] have determined the amino-acid composition of the total proteins in the vitreous humor of the bovine eye by a microbiological method. They point out that these determinations are tentative and have only a restricted value, since the various proteins of the vitreous have not been isolated. Isikawa,[93] as a result of his experiments on certain physical and chemical properties of the two substances, is of the opinion that the hyaluronic acid of the vitreous and the polyuronic acid from the umbilical cord are identical. Using a chromatographic method, Malatesta [94] separated certain keto-acids from the vitreous. A-ketoglutaric and pyruvic acids were found in higher concentrations than in the blood, an observation which may be explained by the high metabolic activity of the retina.

A number of reports [95] have appeared on the microscopic structure of the vitreous. Electron-microscope studies by Matoltsy and co-workers [96] on suspensions of fragmented whole bovine vitreous sediment have demonstrated three distinct types of fibrils and a moderate amount of a fine amorphous material. The most abundant form was a long, thin, curving fibril, suggesting a fine axial repeating period. The second type, which was more curved and definitely striated, was characterized by a repeating axial period of about 610A. The least abundant type appeared to be identical with collagen.

Persistent Hyperplastic Vitreous.—Persistence of the tunica vasculosa lentis has been mentioned recently with increasing frequency in connection with retrolental fibroplasia. It is not related to retrolental fibroplasia in any way but, according to Reese,[97] is the condition most frequently mistaken for it. Its unilaterality and the presence of a persistent hyaloid artery, when visible, are important distinguishing features. The opaque tissue in the vitreous is most dense centrally, and long ciliary processes are always in evidence peripherally. Rupture of the posterior capsule of the lens eventually results in total cataract, and the accompanying swelling of the lens may produce secondary glaucoma.

Cysts of the Vitreous.—Gordüren [98] reports the finding of two cysts, associated with pigmentary disturbances, in the vitreous of a subject with moderately high

92. Schaeffer, A., and Murray, J.: Amino Acid Composition of the Tissue Proteins of the Cornea, Sclera, Vitreous and Retina, A. M. A. Arch. Ophth. **44**:833-841 (Dec.) 1950.

93. Isikawa, T.: Biochemical Studies on Carbohydrates: CXL. On Mucoitin from Vitreous Humor, Tohoku J. Exper. Med. **54**:81-84, 1951.

94. Malatesta, C.: L'analisi quantitativa dei chetoacidi nel vitreo umano e di bue, Boll. ocul. **29**:480-483, 1950.

95. Schwarz, W.: Elektronenmikroskopische Untersuchungen über die Glaskörperstrukturen im Rinderauge, Ztschr. Zellforsch. u. Mikr. Anat. **36**:46-61, 1951. Schuchardt, E., and Knoch, M.: Elektronenmikroskopische Befunde am Glaskörper des Auges, Naturwissenschaften **37**:426, 1950. Schwarz, W., and Schuchardt, E.: Die Struktur des frischen Glaskörpers, Untersuchungen im Phasenkontrast-, Dunkelfeld- und Immersions-Ultramikroskop, Ztschr. Zellforsch. u. Mikr. Anat. **35**:293-310, 1950.

96. Matoltsy, A. G.; Gross, J., and Grignolo, A.: A Study of the Fibrous Components of the Vitreous Body by the Electronmicroscope, Proc. Soc. Exper. Biol. & Med. **76**:857-860, 1951.

97. Reese, A. B., and Blodi, F. C.: Retrolental Fibroplasia, Am. J. Ophth. **34**:1-24, 1951.

98. Gordüren, S.: Cysts of Uveal Origin in the Vitreous, Brit. J. Ophth. **34**:749-751, 1950.

myopia. Because of the location of the cysts and the characteristics of the pigment, the author expresses the opinion that the cysts are congenital and of uveal origin. Cati [99] reviews 18 cases and presents an additional case of nonparasitic vitreous cysts. He favors the view that these cysts originally derived from the anterior retinal layers.

Detachment of the Vitreous.—According to Posner,[100] the sudden appearance of vitreous opacities accompanied with slight haziness of the vitreous and the fundus should suggest the diagnosis of detachment of the vitreous, rather than choroiditis, retinal detachment, or hemorrhage. A definite diagnosis is made by the use of the slit lamp and the Hruby lens. Ophthalmoscopically visible opacities located in the posterior hyaloid membrane permit the diagnosis to be made without the slit lamp, but it is not possible to diagnose the lesion in all cases in this manner, as vitreous opacities are not always present with the detachment. Vitreous detachment is not uncommon and only infrequently is associated with retinal detachment. On the other hand, vitreous detachment is an accompanying feature of every case of idiopathic retinal detachment, and its absence speaks against a simple detachment and in favor of a retinal cyst or choroidal tumor.

Schepens [79] has called attention to the condition of massive vitreous retraction, which appears to be a prime cause of blindness in aphakic eyes in which retinal detachment has occurred. He tentatively suggests that the condition is due to a disturbance of the hyaloid membrane, which causes it to remain adherent to the retina and undergo shrinkage. Diagnosis is made with the ophthalmoscope by the finding of fixed retinal folds which radiate from the posterior pole to the equator. There seems to be no question that aphakic eyes with detachment are oftener affected with detachment than are phakic eyes. Patients under the age of 50, patients who have had loss of vitreous, and patients with detachments of long-standing seem to be particularly predisposed. No form of therapy has been successful.

Hemorrhage into the Vitreous.—Shafer [101] describes a case of vitreous hemorrhage which occurred seven months after a cataract operation. Therapy consisted in the withdrawal and return of about 2.5 cc. of relatively clear vitreous from the eye. A red reflex was first noted in the eye four days after operation, and within two weeks the vision was 20/50. The author states that the notable improvement resulted from the making of more blood products available for absorption.

Sykowski [102] presents a follow-up study on a previously reported case of Eales's disease in which a three-month course of streptomycin was given. No new retinal hemorrhages have been observed in this patient for over two years. In another case, in which the diagnosis of retinitis proliferans with tuberculin sensitivity was made, streptomycin appeared to be beneficial. Corréa de Barros [103] treated a patient with

99. Cati, P.: Cisti non parassitanie mobili nel vitreo, a proposito di un caso personale, Boll. ocul. **30**:161-178, 1951; abstracted, Am. J. Ophth. **34**:1479, 1951.

100. Posner, A.: Detachment of the Vitreous, Eye, Ear, Nose & Throat Monthly **30**:212-213, 1951.

101. Shafer, D.: Hemorrhage into the Vitreous: Aspiration of Vitreous with Reintroduction of Same Vitreous, Arch. Ophth. **44**:748 (Nov.) 1950.

102. Sykowski, P.: Streptomycin in Eales's Disease, Am. J. Ophth. **34**:889-890, 1951.

103. Corréa de Barros, E.: Un cas d'hémorragies récidivantes dan le vitré, traité par la streptomycine, Ophthalmologica **119**:315-317, 1950.

Eales's disease with streptomycin after the onset of proliferative retinitis. Although a hemorrhage occurred eight days after the treatment was started, the progress of the condition since that time seems to have been checked.

Experimental Infections of the Vitreous.—Sorsby and Ungar [104] produced staphylococcic infection of the vitreous by the direct injection of organisms. Treatment consisted in the retrobulbar or subconjunctival injection of penicillin. As a result of their studies, the authors recommend that if vitreous infection is suspected, 1,000,000 units of crystalline penicillin with 5 minims (0.06 cc.) of 1 : 1,000 epinephrine hydrochloride in 1 cc. of water be administered subconjunctivally at the earliest possible time and repeated in 24 hours, if necessary.

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104. Sorsby, A., and Ungar, J.: Control of Experimental Infections in the Vitreous by Penicillin, Brit. J. Ophth. **34**:645-654, 1950.

Correspondence

OPTOKINETIC RESPONSES

To the Editor:—In a recent paper (An Experimental Study of Optokinetic Responses, *A. M. A. Arch. Neurol. & Psychiat.* **47**:43-54 [Jan.] 1952), Hendersen and Crosby report observations on the monkey that are at variance with observations which we have made on human beings. They report that the monkey may inhibit the optokinetic response so long as he is alert and his frontal lobes are intact. Lag of attention or progressive stupor appears to enhance the optokinetic response. With human beings the reverse appears to be the case. The normally alert person is unable to arrest the optokinetic response, so long as it is being properly tested, and lag of attention decreases it.

Stimulated by the discrepancy between their findings and ours, we set out to make comparative observations on monkeys and human subjects. Our procedure differed from theirs in that a large drum, measuring approximately 22 in. (55.9 cm.) in diameter, was placed over the subject's head and illuminated from within, so that practically the entire field rotated. Observations were made through holes drilled in the side of the drum, permitting the examiner to see the subject. The room outside the drum, however, was dark, so that the subject could not see the examiner. We felt that a large drum was essential to insure fixation on the moving stripes; this does not necessarily imply a greater physiologic stimulus.

Our findings in the two monkeys which were available to us were similar to those reported by the authors in that the normally alert monkey gives either no optokinetic response or, at best, poorly sustained and erratic responses. Human beings, however, show invariably a well-sustained optokinetic response, which they cannot arrest under the same conditions of testing.

This basic difference in the optokinetic responsiveness of normal monkeys and man must be borne in mind in drawing conclusions based on observations on one species. While the authors believe they have demonstrated the parts of the brain which are responsible for inhibition of the optokinetic response in monkeys and, by inference, in man, human beings do not appear to have any such inhibitory control. Absence of inhibition is demonstrable by the simple experiment described above, wherein a person is placed in a revolving cylinder and asked to keep his eyes immobile, although open. This he cannot do unless there is some stationary object to fixate on.

A further discrepancy between their observations on the monkey and ours on human beings exists in the alteration in the optokinetic response with unilateral cerebral lesions. They conclude that such a lesion results in a defect of the response when the drum is rotated to the side *opposite* the lesion. We have not made any observations on monkeys with unilateral cerebral lesions, but we would repeat that when there is an asymmetry of the optokinetic response due to a unilateral cerebral lesion in human beings, the deficiency is, with remarkable uniformity, elicited on moving the field *toward* the side of the lesion.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

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April 19, 1951

Isolated Bilateral Abducens Paralysis: Report of a Case. Dr. Robert A. Groff and (by invitation) Dr. Harold Rosegay, Phoenixville, Pa.

Bilateral paralysis of the abducens nerve is caused by various etiologic processes, and may conveniently be divided into two types. The first is caused by direct involvement of the nucleus in the brain stem and/or the nerve by a specific pathologic entity, such as a toxin or an inflammatory or neoplastic process. In this type, there are, in addition to the bilateral paralysis of the abducens nerve, a number of neurologic signs due to the involvement of neighboring structures by such conditions as diabetes, myasthenia gravis, pontine tumors, multiple sclerosis, measles and mumps, encephalomyelitis, epidemic encephalitis, the bilateral Gradenigo syndrome (petrous osteomyelitis or meningitis with bilateral abducens paralysis), thrombophlebitis of the lateral sinus, basilar meningitis, syphilis, nasopharyngeal carcinoma, and lymphocytic leukemia. Congenital paralyses of the abducens facial nerves are seen in Möbius' syndrome, or facial diplegia.

In the second type, an isolated paralysis of both abducens nerves, the cause is either stretch or traction upon the nerves secondary to dislocation of the brain stem. Obviously, this condition is rare. The vulnerable portion of the nerve is between the point at which it leaves the brain stem and the point at which it enters the dura to traverse the wall of the cavernous sinus. Dislocation of the brain stem posteriorly, by either trauma or tumor, would readily affect this portion of the nerve. Cases of isolated abducens nerve paralysis have been reported after cranial trauma and lumbar puncture and in association with some lesions of the posterior fossa. Bilateral abducens paralysis due to traction on the nerve may also occur as a late and remote effect of brain tumor with increased intracranial pressure.

A case of isolated bilateral abducens paralysis due to an interpeduncular teratoid tumor, presumed to represent abducens palsy due to stretch on the nerve, was presented.

DISCUSSION

Dr. Robert A. Groff: The patient was referred to us with the diagnosis of possible brain tumor, with double vision as the only symptom. On examination, the patient presented bilateral paralysis of the sixth nerve and curious nystagmoid movements, about which Dr. Spaeth will have something to say. At operation, we saw no evidence of tumor and had the startling experience of having the respiration stop when the lower left side of the medulla was being inspected. At autopsy, the unusual location of the tumor, in the interpeduncular space, was revealed.

Dr. Rosegay's explanation of the paralysis as due to stretch on the nerves by the tumor and the curious course of those nerves is a plausible one for the paralysis of the abducens nerves. I understand that such an explanation was made many years ago.

Dr. Edmund B. Spaeth: The presence of horizontal and vertical nystagmus in the presence of bilateral sixth-nerve paralysis is remarkable. The nystagmus appeared from the position of the paralytic convergence and continued from the midline into contralateral rotations to the right or the left, the nystagmic movement being from the state of pathologic convergence to the midline.

DR. FRANCIS HEED ADLER: Two years ago a patient was brought to me with what appeared to be concomitant squint but which proved to be bilateral paralysis of the sixth nerve. This patient, a girl aged 8 years, had had a convergent squint for several years and was referred by an uncle whom I had seen in the office several months previously for an old paralysis of the lateral rectus.

On examination, the child showed what appeared to be a concomitant squint, although the abduction of each eye was not complete. The possibility of paralysis of the lateral rectus was ignored at the time. The child had hypermetropia of approximately 3 D. and some blurring of the disks, which was thought to be pseudoneuritis. She was given glasses and treated for concomitant accommodative squint, with no improvement.

During the next three months the blurring of the disk margins increased, and she complained of increasing headache, accompanied with nausea and vomiting. It was then realized that the pseudoneuritis was the beginning of true choked disks, and the child was admitted to the University Hospital as a brain-tumor suspect. Operation revealed a glioma, of which she subsequently died.

The point I wish to make is that bilateral lateral-rectus paralysis, if equal on the two sides, can give rise to a picture which simulates concomitant squint, and that if, as in this case, there is a history of squint in the family and other signs usually seen in accommodative convergent squint, the true nature of the condition may be overlooked.

DR. GLEN G. GIBSON: We are indebted to Dr. Rosegay for bringing us this instructive neuro-ophthalmologic case report. He has illustrated, first, that many of the signs in neuro-ophthalmology are unreliable for the localization of lesions. The most unreliable localizing sign is sixth-nerve paresis, whether unilateral or bilateral. When a sixth-nerve paresis is not associated with other signs, one is frequently at a loss to localize the lesion, since the paralysis may be due to remote pressure or to stretching of the nerve.

Dr. Groff was extremely unfortunate in having a case of interpeduncular lesion with none of the localizing signs, namely, bilateral third-nerve paresis, bilateral pyramidal-tract signs, and chiasmal involvement. The preoperative diagnosis in this case is difficult to understand, and I should like to ask the authors why, in a case of bilateral sixth-nerve paresis, they should think of an intermedullary lesion or a vascular lesion in the pons.

In such a case would it not be quite likely that pyramidal-tract signs or other evidence of intramedullary involvement would be present?

DR. ROBERT A. GROFF: Usually, yes.

DR. GLEN G. GIBSON: The commonest cause of bilateral sixth-nerve paresis in my experience is a nasopharyngeal malignant neoplasm, which should always be ruled out. This lesion was in exactly the place where one would expect a nasopharyngeal malignant growth to penetrate, i. e., the base of the skull. Another condition which is considered a common cause of bilateral sixth-nerve paralysis is craniopharyngioma. In the past 20 years I have seen only one case of craniopharyngioma which was associated with bilateral abducens paralysis.

Some years ago, when the diagnosis of brain tumor was made later in the course of the disease than it is now, it was fairly common experience to encounter cases of bilateral sixth-nerve paralysis associated with increased intracranial pressure. No localizing significance could be attached to the paresis. I note that the authors were careful to state that there was no increased intracranial pressure in their case.

DR. HAROLD ROSEGAY, Phoenixville, Pa.: The diagnosis of pontine glioma, of course, would be untenable. We, rather, had in mind a meningioma *en plaque* under the pons which was pressing against the clivus. That is what I meant by pontine tumor. Vascular thrombosis is unlikely, too. We discussed the possibility that the case was similar to Dandy's case of aneurysm of the vertebral artery, for the child did have sudden onset of diplopia and the isolated abducens paralysis.

Aspiration Biopsy of Malignant Melanoma of Choroid. DR. M. LUTHER KAUFFMAN, Jenkintown, Pa.

A patient had severe retinopathy in the left eye, complicating angiosclerosis and diabetes mellitus, with only 1/60 vision in this eye. In the right eye a large lesion just above the macula, extending far into the vitreous, aroused suspicion. In the vain hope that the lesion might be benign, a biopsy specimen was obtained by inserting a needle into the globe behind the equator and above the tendon of the external rectus, and across the vitreous into the lesion. The stilette was withdrawn, negative pressure applied to the needle, and material withdrawn with the needle. Malignant cells were demonstrated, and the eye was enucleated. A melanoma of a low degree of malignancy was revealed at the final pathologic study. The man died nine months later of a cerebrovascular accident, with no manifest metastasis or local recurrence.

DISCUSSION

DR. A. D. WALLIS: This case is an extremely unusual, if not unique, example of the increasing use of spreads or smears of cells in the diagnosis of malignant neoplasms. The usual criteria on which one relies in most examinations of this sort, as of the common smears of vaginal and bronchial secretions, could not be depended on in this case. Nuclear changes are the basis for decision. The nucleus must be greatly enlarged or highly hyperchromatic or both for the cell to be recognized as malignant. In some tumors, as in the present one, the nuclei are rather uniform. In this case, therefore, Dr. Kauffman and I had to rely heavily on circumstantial evidence.

(A smear made at the operating table was shown.) In this smear, the cells are often polygonal. The nuclei as seen at this moment seem far more variable than they did under the microscope. In some fields there were cells which were definitely pigmented. Knowing that there was a mass, and that that we found cells of a type which we do not expect in the normal retina, particularly those accompanied with pigment, we concluded that in all probability the tumor was a malignant melanoma.

(A section of the tumor after enucleation of the eye was shown.) The cell type is uniform; the cell is polygonal with a fair-sized, not deeply stained, nucleus, very little vascularity, and considerable pigment, in irregular distribution. This tumor can be classified as the spindle cell melanoma, type A, of Callender, which is the least malignant of the melanomas of the choroid.

Among the peculiarities of these tumors, as you know, are their tendency to assume a dumbbell shape, their rarity in the Negro (a fact which, so far as I know, has never been explained), the infrequency of local extension in the orbit, their resistance to radiation, and, particularly, the late occurrence of metastasis, in some cases many years after enucleation. I think a case was reported in which death occurred 19 years after enucleation.

Dr. Kauffman and I were discussing the use of the term leucosarcoma for the melanoma which is without pigment, and apparently this is an accepted term in ophthalmology. To a pathologist it is not a happy one. I am not sure how to classify these tumors. Are they carcinomas or sarcomas? We encounter the same difficulty in the case of melanomas of the skin. There are two schools of thought. I should prefer to speak of the type without pigment as amelanotic melanoma.

DR. WILLIAM ZENTMAYER: Some years ago I had an experience at Wills Hospital that raised in my mind the question whether aspiration is a safe procedure. Of course, what occurred may have been a coincidence. A boy was seen with a suspicious detachment of the retina. Aspiration was done. I do not remember whether or not we were able to make a diagnosis from the procedure. The eye was enucleated, and a few months later a melanoma developed in the orbit; I always suspected that the orbital growth was metastatic as a result of the aspiration, since the choroid was the seat of the malignant melanoma.

DR. JAMES S. SHIPMAN: I am grateful to Dr. Zentmayer for his comment, for on two or three occasions he has deterred me from carrying out this procedure. However, in three cases in which there was doubt as to whether the detachment was solid or serous, and I could not get Dr. Zentmayer to look at the patient, and I was not sure of the diagnosis, I followed this procedure before operating for retinal detachment. In none of these three cases was I able to demonstrate any tumor cells. I proceeded with the electrocoagulation and was able to get the retina back in place. I mention this experience to emphasize that positive results from this procedure indicate the presence of a malignant neoplasm but negative results do not necessarily indicate its absence.

DR. M. LUTHER KAUFFMAN, Jenkintown, Pa.: I wish to repeat that I do not suggest this as a regular procedure. I am fully aware of the dangers of spreading tumor seeds along the tract, and had the patient not had as little as 1/60 vision in the other eye, the procedure probably would not have been considered desirable at all.

Dibenamine®: A Clinical and Experimental Study. DR. SAMUEL L. DELONG (by invitation) and DR. HAROLD G. SCHEIE.

Dibenamine® (N,N-dibenzyl-β-chloroethylamine) is a highly specific and potent sympatholytic and adrenolytic drug, which blocks the excitatory effects of adrenergic stimuli. It has no significant cardiovascular effects except a pronounced orthostatic hypotension with tachycardia. It does not affect the blood pressure in animals or in normal man.

Of five eyes of four patients with acute glaucoma, its administration caused a significant reduction in intraocular tension in three, a questionable reduction in one, and no effect in one.

In diffusion experiments on animals, dibenamine® gave rise to no significant alteration in the amounts of systemically administered substances recovered in the aqueous. Fluorescein sodium was found to appear in the anterior chamber at irregular and inconstant intervals, so that results were considered inconclusive. Only negligible amounts of inulin were recovered in the aqueous of control animals and animals treated with dibenamine.® The amount of systemically administered paraaminohippurate appearing in the aqueous was not appreciably changed after administration of dibenamine.®

Changes in the rate of flow of aqueous from eyes under constant, but slightly below normal, pressure were then investigated. The treated animals showed prompt and significant decreases in the rates of aqueous flow after administration of dibenamine,® while rates of flow in the control animals remained constant or were increased. In control animals, after aspiration of aqueous and replacement with air, the intraocular tension was shown to rise to a level far greater than normal and to remain at this level five hours or more. In experimental series it was demonstrated that the levels to which the tensions rose were significantly lowered in animals which had previously received dibenamine.® Further, when dibenamine® was administered to animals after the "air-block glaucoma" had fully developed, prompt and significant decreases in intraocular pressure were noted.

The authors conclude that dibenamine® is effective in reducing increased ocular tension in man and animals, probably through its sympatholytic properties, which in some way inhibit the secretion of aqueous.

DISCUSSION

DR. HAROLD G. SCHEIE: Dr. DeLong has mentioned that dibenamine® is sympatholytic, blocking the effects of sympathetic stimulation. He also has presented evidence which confirms its effect in lowering increased ocular tension in man and in animals as well. He suggests that it acts through inhibiting the production of aqueous. This assumption is supported somewhat by the aqueous-flow experiments which he cites, as well as by the fact that in man and experimental

animals abnormally increased ocular tension could be reduced by the administration of dibenamine,® and that in animals an induced rise was never as high in eyes of dibenamine® animals as in control animals. The elevated pressure in animals was presumably mechanical, resulting from obstruction of outflow of aqueous; for that reason, dibenamine® should have exerted its effect by lowering the peak level to which aqueous could be secreted into the eye.

Because the effect of dibenamine® in reducing ocular tension cannot be correlated with changes in blood pressure, a local ocular action is the most likely explanation. Several possibilities have been suggested or come to mind.

1. Swan showed that it was not related to an effect upon the intraocular muscles, because there is no relation between pupillary size and its effect on tension.

2. It is also possible that dibenamine® might affect the osmotic relationships between the plasma and the intraocular fluids, with the result that fluid is drawn from the eye, but there is no evidence to indicate this.

3. The most likely possibility remaining is that which ties in with the evidence presented by Dr. DeLong, that is, an effect upon aqueous flow.

This could be brought about by changes in capillary pressure and permeability, even though the systemic blood pressure had not changed. In our experiments, we found no evidence to indicate significant change in permeability of the blood-aqueous barrier. It tended to support, instead, Friedenwald's hypothesis that epinephrine plays a role in the mechanism of aqueous production and that somehow this action is blocked by dibenamine.® At any rate, the only positive evidence which we found in our experiment was that pointing toward diminished production of aqueous.

Warren S. Reese, M.D., *Chairman pro Tem*

M. Luther Kauffman, M.D., *Clerk*

Oct. 18, 1951

Mixed-Cell Tumor of the Lacrimal Gland: Report of a Case. DR. CHARLES G. STEINMETZ III (by invitation).

Tumors of the lacrimal gland are uncommon, and mixed-cell tumors constitute the majority. A carcinoma of the lacrimal gland may represent a mixed tumor which has become carcinomatous after recurrence or has been carcinomatous from the beginning. Two types are generally recognized: (1) true mixed tumors (rare), and (2) essentially epithelial growths of various types which may or may not show myxomatous stroma. Exophthalmos is the chief complaint in 80% of cases. Edema of the lids is secondary; diplopia may occur, and exposure keratitis may develop later. The treatment is surgical, as these tumors are resistant to radiation. The incidence of recurrence, even after surgical extirpation, is 100%.

The patient whose case is reported was first seen at the Wills Hospital in 1947 at the age of 17. He had a history of trauma to the head 7 years before admission and of unilateral proptosis with onset 10 days prior to admission. There was no pain or loss of visual acuity. Studies revealed nothing significant, and the 5 mm. of proptosis in the left eye subsided spontaneously nine days after the patient's admission. The patient then entered the Army and in December, 1948, again had painless proptosis of the left eye, which again subsided spontaneously, after eight weeks. The clinical impression was that of hemangioma. The patient was asymptomatic until May, 1951, when he experienced a recurrence of previous symptoms, with diminution of visual acuity (6/6 in the right eye and 6/15 in the left eye). The results of all studies were normal except for an exophthalmometric reading of 22 mm. in the right eye and 29 mm. in the left eye. Proptosis remained constant, but the chemosis became progressively worse. A tumor was palpated in the upper temporal quadrant of the left orbit. A Krönlein approach revealed a tumor of the lacrimal gland. The

diagnosis of adenocarcinoma was made by the staff pathologist; two other pathologists did not accept this diagnosis. Proptosis receded, and visual acuity returned to 6/6. The patient is being kept under observation.

The case of mixed-cell tumor was characterized by painless proptosis, diplopia, a long duration, and difficulty of final diagnosis.

DISCUSSION

DR. I. EDWARD RUBIN: I presented a similar case before this section in 1948, that of a man aged 36, who at the age of 16 had had a tumor of the lacrimal gland removed by Dr. Zentmayer. The pathologic diagnosis was mixed-cell tumor of the lacrimal gland. This tumor recurred 12 years later and was treated with x-rays. Five years later the tumor was excised, and again the pathologic report was mixed-cell tumor of the lacrimal gland. However, the tumor soon recurred, causing ptosis of the left upper lid and proptosis of the left globe. At the age of 35 the recurring tumor was again removed, and the diagnosis was then adenocarcinoma of the lacrimal gland. The left orbit was exenterated, but the patient died a year later of extension of the malignant growth to the adjacent bone and the brain. There was also metastasis to the ninth rib on the left side.

I should like to stress that a tendency of mixed-cell tumors of the lacrimal gland to recur will be found if they are followed for a long time, and they tend to become malignant after many years.

X-ray therapy has little effect on the tumor. If the tumor invades the soft tissue of the orbit, immediate exenteration is indicated. If there is involvement of bone, complete resection of the involved osseous portion should be carried out.

Some of the photomicrographs shown by Dr. Steinmetz appeared to be adenocarcinoma. I suggest that more blocks be cut from the pathologic specimen and that the new slides be carefully reviewed for malignant changes. Nevertheless, the patient should be kept under observation for many years for possible recurrence.

DR. GEORGE F. J. KELLY: It is my understanding that early in this case there were signs of involvement about the eye with proptosis. Later there was recession. Can you suggest any explanation of this? Unless something intervenes to alter it, the course of a tumor is usually relentless and progressive.

DR. CHARLES G. STEINMETZ III: Dr. Kelly has presented some good questions. I doubt whether I can answer them.

This case is very similar to one presented by Dr. I. J. Eisenberg at the Wills Hospital conference about two years ago. The latter patient was a woman in her 30's who had had a tumor removed from the orbit seven years prior to her last admission. The tumor was diagnosed histologically as hemangioma of the lacrimal gland. The patient was asymptomatic for seven years and then had a recurrence. Dr. Spaeth then removed by the Krönlein operation a large tumor which had extended into the bone. This time, the microscopic diagnosis was lymphosarcoma of the lacrimal gland. On review examination of the original slides, islands of mixed cells were noted. In the case presented by Dr. Steinmetz the diagnosis made in the Army was hemangioma. This was based, not on biopsy, but merely on a clinical impression. However, if the tumor had started as a hemangioma, the possibility of expansion due to engorgement could account for the recurrences. I know of no other rational theory except, possibly, local edema.

Early Results of Perforating Cyclodiathermy in Treatment of Glaucoma. DR. I. EDWARD RUBIN; DR. JOHN E. ROMIG, New York, and DR. J. HUBERT MOLLOY (all by invitation).

Cyclodiathermy was defined as destruction of the ciliary body by diathermy. Diathermy is the therapeutic use of high-frequency current to generate heat within some part of the body. Long-wave and short-wave diathermy and microdiathermy were briefly discussed.

A historical account of perforating cyclodiathermy, starting with Vogt, in 1936, was presented.

The modus operandi of lowering intraocular pressure by cyclodiathermy (surface or perforating) has never been adequately explained. Several theories were mentioned.

This series of 25 patients with glaucoma (13 private patients from the records of Dr. Edmund Spaeth and Dr. William E. Krewson and 12 ward patients from the service of Dr. Spaeth) were treated at the Graduate Hospital with perforating cyclodiathermy according to the technique described by Dr. Ramón Castroviejo in Florida in 1951 (Personal communication from Dr. Castroviejo, Mid-Winter Post-Graduate Course in Ophthalmology, University of Florida, Miami, Fla., Jan. 18-20, 1951). Altogether, the operation was performed on 29 eyes. The technique consisted of using the coagulating current of the Bovie diathermy machine set at 10 on the dial with a special needle point (1.0 by 0.15 mm.). The needle handle was completely insulated except for the short needle-point tip. With the use of local anesthesia, the needle point was inserted through the undissected conjunctiva 5.5 mm. from the limbus for eight seconds. A single row of 16 such perforating punctures was made through the conjunctiva all around the limbus, four punctures being placed in each quadrant. Then paracentesis was performed, and a small air bubble was injected into the anterior chamber. The patient was permitted out of bed on the first postoperative day. The eye was dressed daily with a single dressing, and drops of pilocarpine were instilled once a day. It was recommended that if repeated cyclodiathermy is performed on the same eye, not more than six to eight punctures be made, to prevent the occurrence of hypotension.

The youngest patient was aged 5 years, and the oldest 76 years. The follow-up period varied from 1 to 10 months.

Ten patients with postoperative aphakic glaucoma, that is, 10 patients in whom glaucoma developed after cataract extraction, were treated with perforating cyclodiathermy. The tension was normalized in seven patients; in two the tension remained somewhat elevated but there was relief of pain, and in one the tension fell to 9 mm. Hg (Schiøtz) and remained so to the time of report, for eight months.

Of four patients with absolute glaucoma treated with perforating cyclodiathermy, one had an excellent result; two experienced relief from pain with some reduction in intraocular tension, and one had no relief and her eye was enucleated six days after the cyclodiathermy procedure.

Of a series of four patients with glaucoma secondary to rubeosis iridis diabetica treated with perforating cyclodiathermy, two experienced good results with normalized tension; one had relief from pain, and the result for one was recorded as failure. It is interesting to note in these four patients with rubeosis iridis that as soon as the cyclodiathermy needle was inserted and the current started, the vessels on the surface of the iris disappeared. As soon as the paracentesis was completed, the vessels of the iris reappeared. The perforating cyclodiathermy must have had a strong, but temporary, vasoconstrictor effect.

In two patients with chronic glaucoma associated with aphakia, good results were obtained with the perforating cyclodiathermy. In one of these patients it was necessary to repeat the cyclodiathermy procedure before the tension returned to normal.

Two patients with hemorrhagic glaucoma had good results with perforating cyclodiathermy.

Two children with congenital glaucoma in each eye were also treated with this procedure bilaterally. Both children had good results in each eye.

One patient with chronic simple glaucoma, a Negro woman aged 50, was treated successfully with perforating cyclodiathermy.

Finally, a patient with bilateral glaucoma associated with bilateral iridocyclitis had one eye treated with perforating cyclodiathermy. The result was recorded as poor because the tension fell from 50 to only 36 mm., but there was much less pain in the eye.

In the series of eight Negro patients with difficult glaucoma situations, fairly good results were reported with this procedure of perforating cyclodiathermy.

DISCUSSION

DR. WILLIAM C. FRAYER, Ann Arbor, Mich.: To further the discussion of this paper, I should like to present briefly a series of patients treated by cyclodiathermy at the Hospital of the University of Pennsylvania. All were operated upon by Dr. Harold G. Scheie or by residents under his direct supervision.

The series may be divided into two groups. In the first group of 17 patients who were operated on between 1946 and 1949, the Vogt technique, already described, was employed. Multiple punctures were placed over the bared sclera in a band beginning 3 mm. from the limbus and extending out as far as 7 mm. The longest follow-up period in this group was 53 months. At the time of the last follow-up observation only 7 of the 17 patients showed normal tension. Six of the group showed corneal opacities as a result of cyclodiathermy.

Discouraged by the inconstant control of tension and by the high incidence of corneal damage and disorganization of the angle, Dr. Scheie discontinued the use of cyclodiathermy in 1949. In January, 1951, however, influenced by Dr. Castroviejo's enthusiasm for a newer technique being used in Europe, he again began to perform cyclodiathermy. With this technique, fewer punctures are used; they are placed 6 mm. from the limbus, and the electrode is held in place for a longer period for each puncture. In our patients, a single row of 9 to 12 punctures was made 6 mm. from the limbus, beginning at the lower portion of the medial rectus, extending over the upper portion of the globe, and ending at the lower border of the lateral rectus muscle. A 1-mm. electrode was applied for 10 seconds at each puncture.

Thirteen patients have been operated upon with this technique at the Hospital of the University of Pennsylvania. The longest follow-up period for this group is 10 months, and it is too early to draw any but preliminary conclusions. Of the 13 patients, 2 have been operated on so recently that no follow-up data are available. Of the remaining 11 patients, the ocular tension in 9 was normal after one cyclodiathermy procedure. The other two patients required a second operation, which was then successful in controlling the tension. The second operation was done over slightly more than the lower half of the eye. To date, none of this group of 13 patients shows corneal edema or opacity not present prior to the operation, and the postoperative course seems to have been much quieter than in the original group, treated by the older technique.

DR. THOMAS COWAN: The essayists have given a detailed account of the technique of cyclodiathermy and have presented some optimistic reports on the result of the operation in various types of glaucoma.

As with all new procedures, the operation will have to be done in many cases by many operators before the true value of the procedure can be judged. At the Wills Hospital, in the service of Dr. Spaeth, I have found seven ward patients, operated on by this technique in the last few years, whose cases I should like to present briefly.

In Case 1, that of a white woman aged 57, two cyclodiathermy operations were done at a three-week interval. After temporary improvement, tension rose higher than before, and the eye is now blind, painful, and disorganized, but not phthisic.

In Case 2, that of white woman aged 61, the tension rose higher than before after cyclodiathermy. The eye is now blind but not painful.

In Case 3, that of white woman aged 52, secondary glaucoma followed cataract extraction. Cyclodiathermy was done and then repeated. The tension increased, after a temporary remission. The eye is not painful, but the tension is high, and vision is now limited to perception of hand movements.

In Case 4 a Negro woman aged 60, with secondary glaucoma following uveitis, had a paracentesis, followed by prolapse of the iris through the paracentesis opening. After cyclodiathermy the tension rose for a while and then subsided as partial phthisis bulbi developed.

In Case 5, that of a Negro woman aged 57 with chronic simple glaucoma, intraocular tension decreased after cyclodiathermy, then rose, and then fell again; we thought the condition was cured but at the last examination, yesterday, tension was 31 mm., and I expect it to go up. It is about seven months since the last cyclodiathermy.

In Case 6, that of a patient aged 50, with chronic simple glaucoma, the tension became normalized after cyclodiathermy.

In Case 7, that of a white woman aged 21, tension failed to normalize, and vision was lost.

However, our ample percentage of failures should not be an indictment of this procedure, since most of the eyes were practically hopeless. The success, partial and temporary, in these ocular wrecks is encouraging. The operation is of such extreme simplicity as scarcely to warrant the term "surgery," and it could be performed, I believe, by any tyro in ophthalmology.

If its long-term effects live up to its early promise, glaucoma surgery may very well be revolutionized in the direction of further simplicity. We have not reached this desired goal yet. The operation has been done in too few cases, by too few operators, and the patients have been followed for too short a time. The skeptics, as well as the enthusiasts, will have to be heard from. However, enough success has been achieved to suggest that a surgical principle of great value has been discovered. Especially significant are the favorable results in some of those conditions which had heretofore been considered intractable, especially rubeosis iridis and absolute glaucoma. The technique as outlined by the authors, although easy and a good one, should not be considered the final word. Just as the principle of aqueous drainage through a filtering bleb was found to be a valuable principle, which was exploited through various techniques, so whatever factor is responsible for the success of the cyclodiathermy should, and will, be exploited through many other techniques until its full measure of benefit can be applied.

DR. GEORGE P. MEYER, Camden, N. J.: I should like to ask the obvious question: To what does the University group attribute the differences in the results in their two studies?

DR. WILLIAM C. FRAYER, Ann Arbor, Mich.: In answer to Dr. Meyer's question, perhaps I failed to make the point that in our opinion the difference is the different distance from the limbus; the punctures made in the original technique in the older group with the poorer results were made up to 3 mm. from the limbus, whereas in the newer groups they have all been 6 mm. from the limbus.

DR. E. I. RUBIN: Was paracentesis recommended?

DR. WILLIAM C. FRAYER, Ann Arbor, Mich.: No, sir. It was not.

DR. E. I. RUBIN: I should also like to stress that our follow-up period has been only 10 months. Also, in our opinion, it was extremely important to have the needle point insulated, as Dr. Romig pointed out. He did not mention one case in which we thought the result was very good. A Negro woman of 50 had chronic simple glaucoma of several months' duration. She was blind in one eye and had 6/6 vision in the other eye, with only a 10-degree field. Tension was in the 50's. We used this operation as a primary procedure and now five months later, the tension continues to be normal and vision 6/6, with the 10-degree field, a result which we consider excellent.

Use of Surface Therapy with the Shahan Thermaphore in Treatment of Retinal Detachment. DR. EDWARD S. GIFFORD JR.

In 1934 it was suggested that the Shahan thermaphore applied to the sclera, in conjunction with posterior sclerotomy, might meet the requirements of surgery for retinal detachment. This method was used successfully by H. M. Langdon (*Am. J. Ophth.* **18:** 550, 1935) and by Post (*Am. J. Ophth* **17:** 1122, 1934).

Fourteen patients with simple retinal detachment were operated upon with the Shahan thermaphore at the Pennsylvania Hospital by Dr. Alexander G. Fewell,

Dr. M. Luther Kauffman, or myself. Nine of them obtained complete reattachment, full or nearly full fields, and return to normal vision or the vision the patient had before detachment. Two of the failures were in uncooperative patients.

The conjunctiva is incised, and an applicator, the terminal end of which is a grid 1 cm. square, heated to a constant temperature of 160 F., is applied to the sclera for periods of one minute, until the entire area corresponding to the detachment is covered. The applicator is passed beneath the muscles without cutting them. The subretinal fluid is released by performing a posterior sclerotomy at the site of the retinal tear. If the detachment is extensive, a second sclerotomy is placed where it will do the most good; it may be done before the thermaphore is applied.

This method has a number of advantages: 1. Less trauma to the eye results. 2. The retinal tear need not be so accurately localized, since a large area is affected by a single application. 3. For the same reason, large holes and multiple holes are treated more effectively. 4. Undetected tears have an excellent chance of closure, since the entire area of detachment is covered. 5. The temperature and depth of penetration are uniform. 6. Muscle imbalance cannot result. 7. The thermaphore may be used prophylactically after sclerotomy when an intraocular foreign body is removed by the posterior route.

DISCUSSION

Dr. M. Luther Kauffman, Jenkintown, Pa.: It has been my pleasure and privilege to work with Dr. Gifford on most of these patients, and I can assure you of the ease of performance of the operation. The time required is not too long, a factor which may be important in some cases. The field retention in these patients is very good indeed; that is one of the great advantages of a surgical procedure of this type. The question of whether to release the subretinal fluid before or after the application of heat we solved the hard way. From our experience, we concluded that if the retina has returned to its normal position simply by the patient's lying in bed for several days, it is quite proper to apply the heat before the fluid is drained. This has advantages, for the surgeon has a drier field. However, if the retina has not returned to its normal position, or nearly so, after the several days in bed, it is easily understood that the proper inflammatory reaction is not produced by applying the heat through a fairly thick layer of fluid. In that case, it is quite proper to drain the fluid beforehand. Our experience has taught us that that is the case.

Dr. Thomas Cowan: The results that Dr. Gifford has obtained compare favorably with those in which the much more complicated diathermy machines are used. I should like to ask Dr. Gifford whether he sees any opacities in the vitreous after the operation and, if so, how long they last.

Dr. Edward S. Gifford Jr.: Of course, we do see opacities in the vitreous. In all our cases there have been some, but it is remarkable how few there are some time after treatment in these successful cases. There has been a little vitreous dust remaining in some, and in others the media have been absolutely clear.

I like to recall a case which would have strained the bonds of modesty if it had been included in the paper. A man of 24 with a cryptogenic detachment was operated on in 1941; he was subsequently taken into the Army and became an artillery officer at the Maryland Proving Grounds. As the guns went off, he became a bit alarmed and reported that he had once been operated on for detachment of the retina.

The Army wrote me for confirmation, since he had 20/20 vision, a full field, and clear vitreous and the retinal pigmentation in the region of the ora serrata was visible only with maximum dilation of the pupil. I should say that in half the cases in which the outcome was successful the media were entirely clear.

This method, of course, is not so highly dramatic in its results that it will supplant ignipuncture, but I think it should take equal status with the other methods that are now in use.

News and Comment

EDITED BY DR. W. L. BENEDICT

PERSONAL NEWS

Appointment of Dr. Irving H. Leopold.—Dr. Irving H. Leopold has been appointed an attending surgeon at the Wills Eye Hospital, Philadelphia, succeeding to the service of the late Dr. Louis Lehrfeld, who died on Feb. 6, 1952. Dr. Lehrfeld had served the Wills Eye Hospital over a period of 36 years, until his death.

Books

Synopsis of Ophthalmology. By J. L. C. Martin-Doyle. Price, $4.50. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1951.

This volume is a compendium of the whole field of ophthalmology, with a comprehensive index. It should serve a useful purpose for the general physician and the medical student who wishes to obtain a concise but limited knowledge of diseases of the eye. There are no illustrations.

The material is brought up to date, and there are only a few instances in which criticism can be raised. As an enlarged dictionary of ophthalmology, the book will serve a useful purpose.

The Significance of Heredity in Ophthalmology: A Tasmanian Survey. First Edition. By J. Bruce Hamilton. Price, 50s. A. H. Massina & Co., Pty. Ltd., 350 Swanston St., Melbourne, Australia, 1951.

The author has determined the incidence of inherited ophthalmic diseases and inherited blindness in Tasmania from an analysis of the data on 11,000 patients seen in private practice and on the patients receiving pensions for the blind and patients in the sight-saving schools of Tasmania. The book is not a text on heredity in ophthalmology, but an original investigation from which the author draws certain conclusions.

The book is well documented with tables, summarizing his material, and a list of pedigrees at the end. It will chiefly be of value to those interested in genetics.

A Pathology of the Eye. By Eugene Wolff. Third Edition. Price, $9.50. Pp. 364, with 318 illustrations and 5 color plates. The Blakiston Company (Division of Doubleday & Company, Inc.), 1012 Walnut St., Philadelphia 5, 1951.

This beautifully printed edition of Wolff's valuable book will be welcomed by all interested in the pathology of the eye. The older material has been carefully revised, and such subjects as diabetic retinopathy, retrolental fibroplasia, the origin of the melanomata, and the nature of retinoblastoma have been brought up to date. The author has made splendid use of a number of drawings of microscopic pathology which enable the reader to see at a glance the details referred to in the text. It has been the discouraging experience of the reviewer that only too frequently photomicrographs confuse, rather than elucidate, a text. Apparently, the author has been keenly aware of this, and the photomicrographs which he has chosen to include have been hand-picked and beautifully reproduced. The text is concise but all-inclusive, and covers the entire pathology of the globe and its adnexa.

Lehrbuch der Augenheilkinde. By Dr. Karl Lindner. Price, $6.89. Urban & Schwarzenberg, Frankgasse 4, Vienna IX; Thierschstrasse 11, Munich 22.

It is surprising that no textbook of ophthalmology has appeared from the pen of this internationally famous teacher until now. As is to be expected, this text is a beautifully organized, complete résumé of the field, with special emphasis on diseases of the conjunctiva. The section on trachoma will be of particular interest to ophthalmologists because of Lindner's own work in this field. He relates some amusing incidences in infecting his own eyes with Noguchia granulosis (Bacterium granulosis).

The book is intended for the student of ophthalmology, but contains many sections on treatment which will be of value to the practicing ophthalmologist.

Oftalmologia especial teorica y clinica. By Dr. Manuel Marquez. Price, 140 pesos (about $16.75). Pp. 783, including index, with 680 illustrations, 2 in color. La prensa médica mexicana, Zacatecas 21-25, México, D. F., 1952.

This book is in a sense a condensation and reorganization of the bulk of the author's writings for over half a century. It is a complete, moderately advanced book covering practically all phases of the theory and practice of ophthalmology. In the subject matter the medical, surgical, and optical branches of ophthalmology are well proportioned. While the book is intended mainly for physicians entering the specialty of ophthalmology, it is sufficiently advanced and comprehensive to be of value to those already in practice.

The author has a simple, didactic style, which is mirrored in clarity of expression and strict, logical thinking. One may or may not agree with all his ideas, e. g., his views on the cause and classification of glaucoma, which differ from those generally given, or his evaluation of the various cataract operations and the generally accepted operative techniques. But one knows exactly what one can agree with and what one can disagree with, as the author's views are definite and clear-cut.

The book is richly illustrated with figures, diagrams, and photographs. Throughout, one feels the master hand of the author, who writes from an unusually rich experience as a background for sound theoretical expositions. Physicians with a reading knowledge of Spanish will be intrigued and stimulated by this work.

CORRECTION

In the article entitled "Effects of Ultrasonic Waves on the Refractive Media of the Eye" by Dr. Oscar Lavine and his associates, published in the February A. M. A. ARCHIVES, the sentence beginning on the eighth line of page 218 and the following sentence should read: "These opacities were reversible, although even after periods of as long as an hour there were enough remaining bubbles to outline the region in which they had been most numerous immediately after irradiation. Figure 9 shows these Zeiss cataracts."

OPTICIANRY CLINIC NOTES

OPHTHALMIC PROBLEMS AND DEVELOPMENTS

A COMPLETE RANGE OF ABSORPTION IN *Soft-Lite Lenses*

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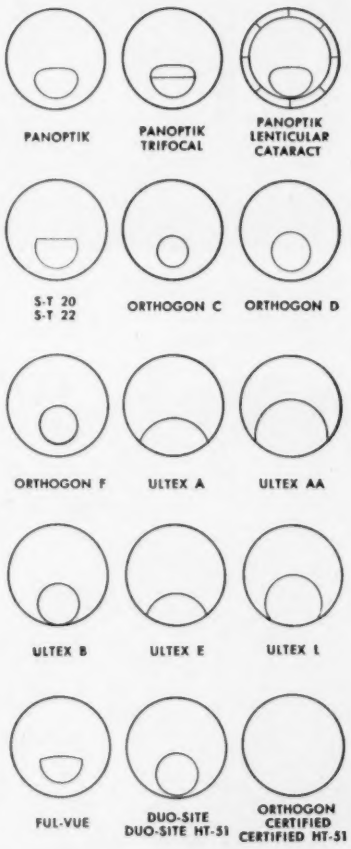

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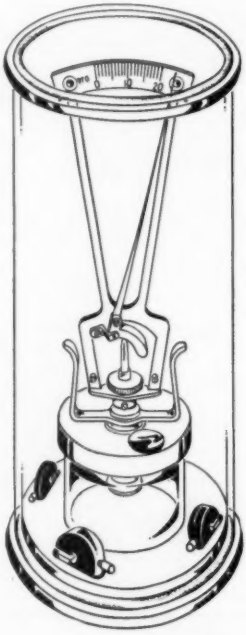

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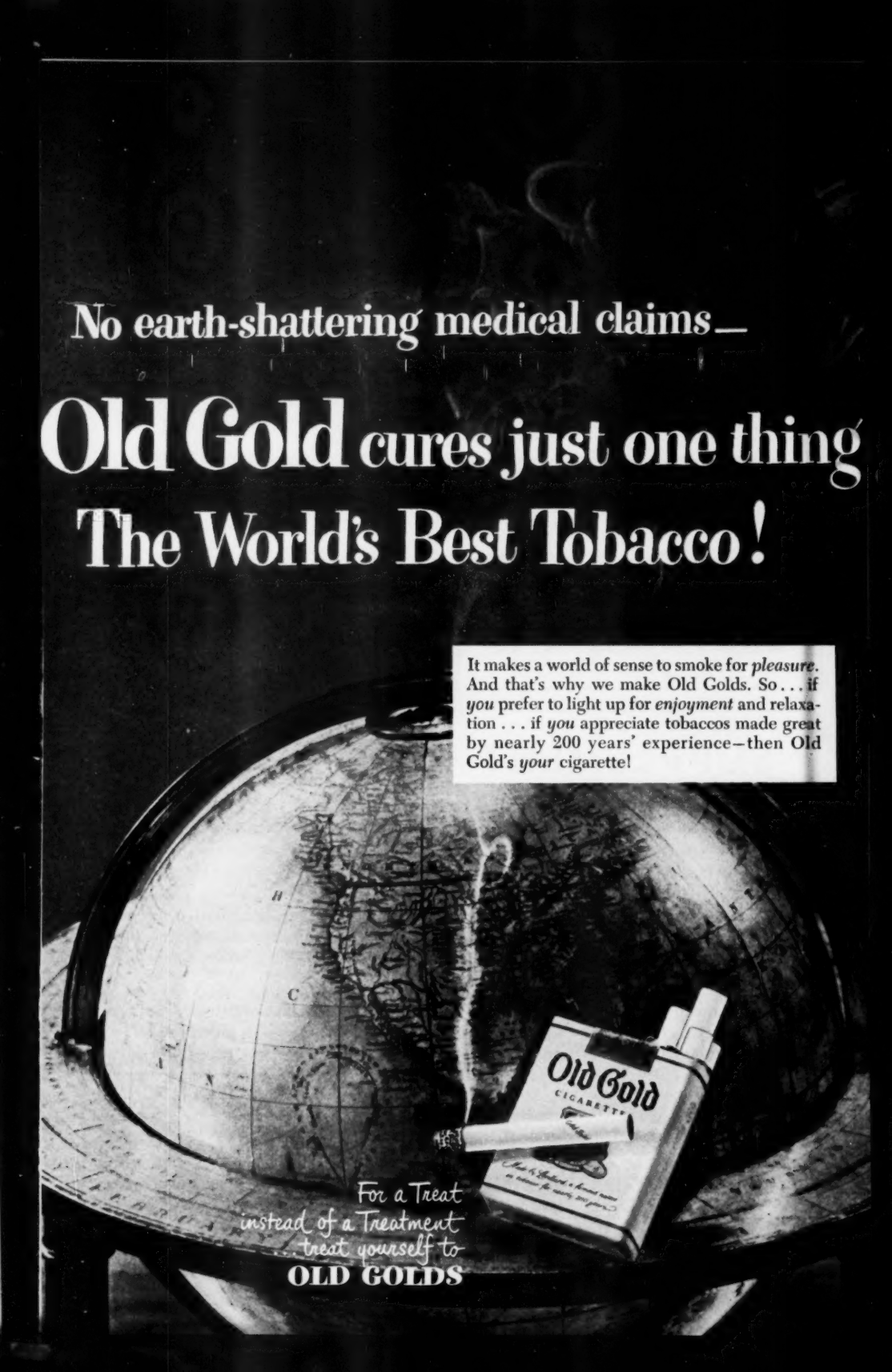
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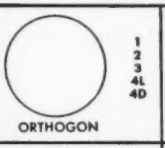
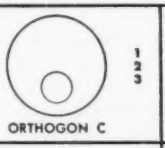
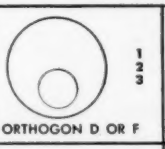
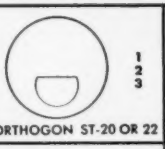
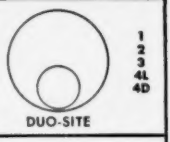
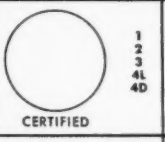
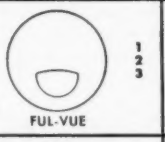
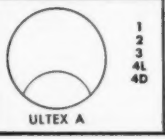
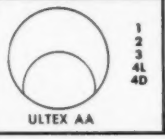
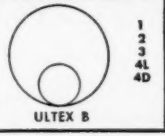
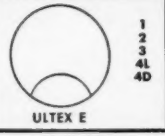
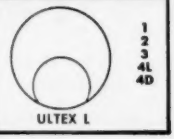
 ORTHOGON 1 2 3 4L 4D	 ORTHOGON C 1 2 3	 ORTHOGON D OR F 1 2 3	 ORTHOGON ST-20 OR 22 1 2 3	 DUO-SITE 1 2 3 4L 4D
 CERTIFIED 1 2 3 4L 4D	 FUL-VUE 1 2 3	PANOPTIK 1 2 3	PANOPTIK TRIFOCAL 1 2 3	PANOPTIK LENTICULAR CATARACT 1 2 3
 ULTEX A 1 2 3 4L 4D	 ULTEX AA 1 2 3 4L 4D	 ULTEX B 1 2 3 4L 4D	 ULTEX E 1 2 3 4L 4D	 ULTEX L 1 2 3 4L 4D

1 You have determined the sphere, cylinder, prism and other lens correction data. You have used the subjective glare symptom questions and the Trial Case Accessory to determine the patient's degree of light sensitivity.

2 You have found that a general purpose *neutral* absorptive lens is indicated, rather than an occupational ultra-violet-selective filter.

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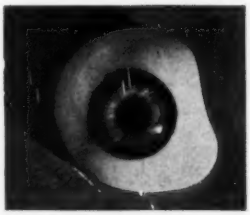

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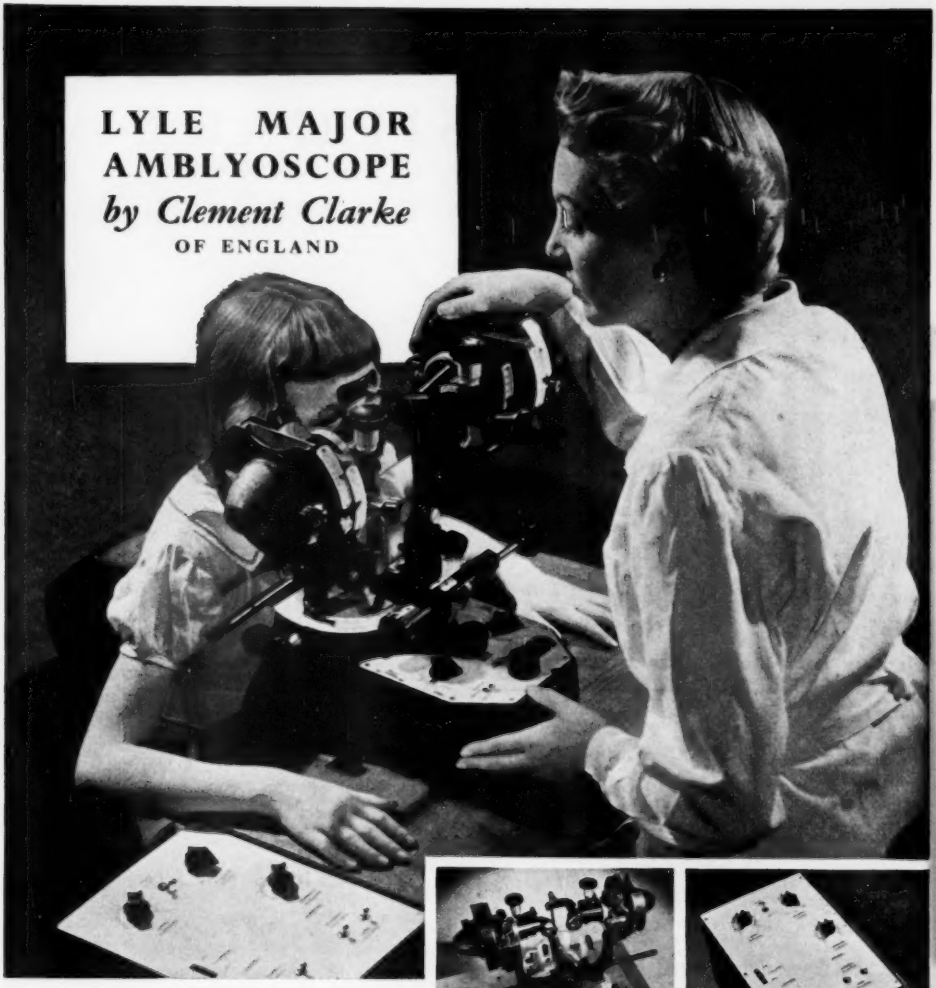

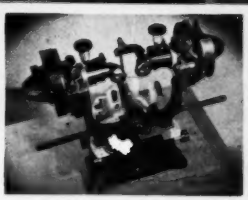

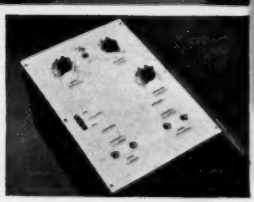

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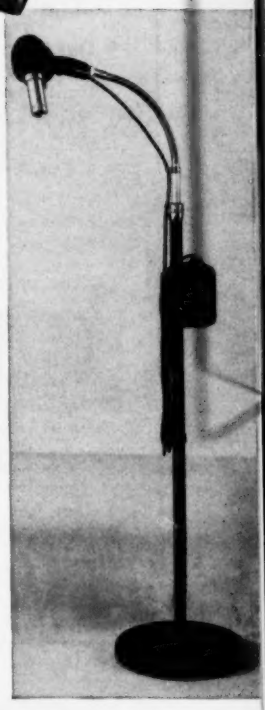

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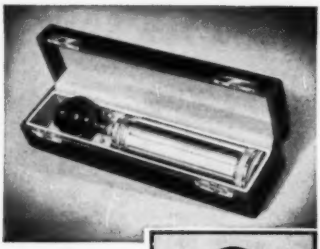

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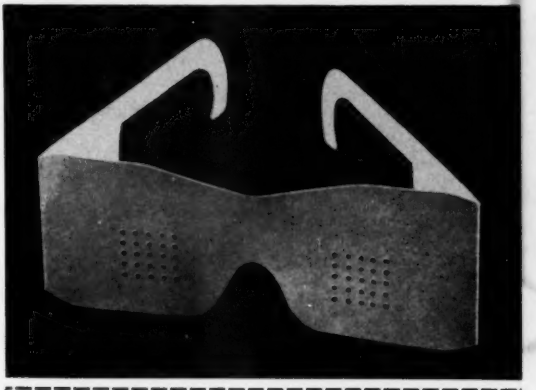

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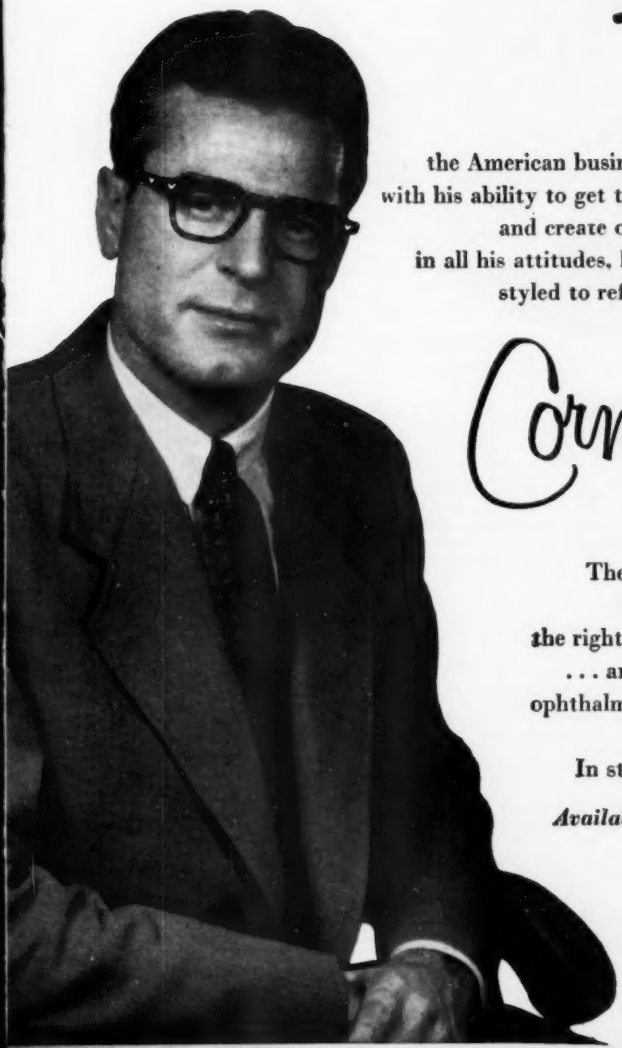

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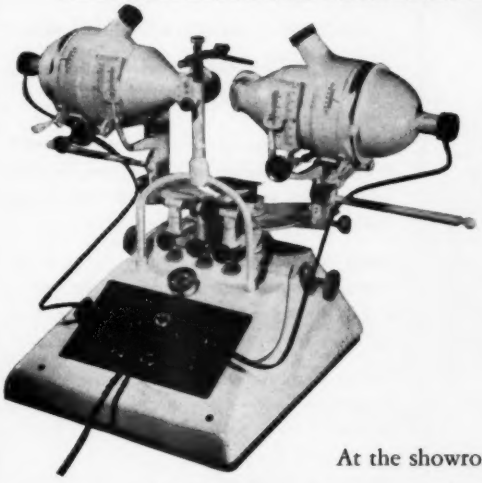

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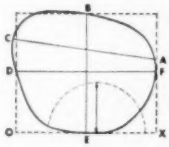

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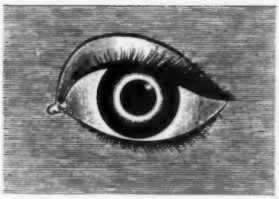

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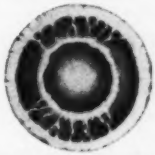

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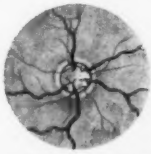

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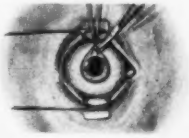

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